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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL

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July 22, 2017
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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HENRY C. NIPPER, Ph.D.	Temporary Panel Member
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M E E T I N G

(8:07 a.m.)

DR. WATSON: Good morning, everyone. I would like to call this meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee to Order. I'm Dr. Karol Watson. I'm a cardiologist, full professor at UCLA School of Medicine.

I would like to ask the Panel to introduce themselves. If we could start from this corner?

DR. HENDERSON: Yes. Okay. Hi, I'm Cassandra Henderson. I am a physician and a certified diabetes educator. I am Director of the High-Risk Service at Lincoln Medical Center in the Bronx, and I'm a professor at Cornell Medical College in the Department of Obstetrics and Gynecology.

DR. NIPPER: Hello. I'm Dr. Henry Nipper. I'm a Ph.D. clinical chemist, board certified by the American Board. I'm professor of pathology at Creighton University in Omaha, Nebraska.

DR. McSHANE: I'm Lisa McShane. I'm the Chief of the Biostatistics Branch in the Division of Cancer Treatment and Diagnosis at the National Cancer Institute. I specialize in biomarkers and in the evaluation of assays.

DR. WYNE: Kathleen Wyne. I'm an adult endocrinologist at the Ohio State University.

DR. BURR: Good morning. It's Friday. It can't be all bad. My name is Bob Burr. I'm an endocrinologist in independent practice in Salt Lake City.

LCDR GARCIA: Good morning. My name is Patricio Garcia. I'm the Designated Federal Officer for this meeting. Thank you.

DR. KWONG: Good morning. I'm Tai Kwong. I'm from University of Rochester,

where I'm professor of pathology and laboratory medicine and also the Director of the Hematology/Chemistry Laboratory.

DR. REMALEY: Hi, my name is Alan Remaley. I'm a pathologist in the Department of Laboratory Medicine at NIH and a senior investigator in the Heart, Lung and Blood Institute.

DR. GOLDSMITH: Thank you. Good morning. I'm Barbara Goldsmith, a full professor in the Department of Pathology, Anatomy and Cell Biology at Thomas Jefferson University. I'm also Director of Point-of-Care Testing and Quality for the department. I also wear another hat there, and that's Chair of the Department of Medical Laboratory Sciences and Biotechnology in the College of Health Professions.

DR. REJ: Good morning, everybody. I'm Bob Rej. I'm Director of Clinical Chemistry and Hematology for the Wadsworth Center, the public health laboratory for the State of New York in Albany, and also Associate Professor of Biomedical Sciences in the School of Public Health at the State University of New York in Albany.

MS. McCOLLISTER-SLIPP: I'm Anna McCollister-Slipp. I'm here as a Patient Representative. I've had type 1 diabetes for 30 years.

MS. DAIGLE: Good morning. I'm Patricia Daigle, nurse practitioner for LSU Medical School. I am here as the Consumer Representative.

MR. THURAMALLA: Good morning. I'm Naveen Thuramalla. I work as the Vice President for Regulatory Affairs at ARKRAY, Incorporated. Today I'm serving as the Industry Representative. Thank you.

DR. WATSON: Thank you, Panel. Welcome all.

I note for the record that the Panel members in attendance constitute a quorum, as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations on information regarding the 510(k) premarket approval application for Alere Afinion Hemoglobin A1c Diagnosis test system device. The issue to be discussed in this meeting is the Sponsor's proposal to change the intended use to be used in moderate complexity point-of-care setting for the quantitative determination of glycated hemoglobin (hemoglobin A1c) in fingerstick and venous whole blood as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes.

Before we begin, I would like to ask all the distinguished Panel members and FDA staff seated at the table -- oh, we already did. Sorry.

For members of the audience, if you have not already done so, please make sure you sign in, in the sign-in sheets that are located by the doors.

Lieutenant Commander Patricio Garcia is the Designated Federal Official for this meeting, and he will make some introductory remarks now.

LCDR GARCIA: Thank you, Dr. Watson.

The Food and Drug Administration is convening today's meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations. The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress

has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purpose of 18 U.S. Code, Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations on the information regarding the premarket notification 510(k) submission for the Alere Afinion HbA1c Dx point-of-care test system sponsored by the Alere Technologies AS. Current clinical guidelines contraindicate the use of point-of-care hemoglobin A1c test to diagnose diabetes. FDA is seeking feedback from the clinical community to determine significant, scientific, and practical reservations or support for using this point-of-care HbA1c test as an aid in the diagnosis of diabetes and pre-diabetes.

Based on the agenda for today's meeting, all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208.

Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry, and is employed by ARKRAY, Incorporated.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from

such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firm at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Thank you.

Before I turn this meeting back over to Dr. Watson, I would like to make a few general announcements. Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. Information on purchasing videos of today's meeting can be found on the table outside the meeting room. Handouts of today's presentation are available at the registration desk.

The press contact for today's meeting is Lyndsay Meyer, and she's standing in the back.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you would like to present during today's Open Public Hearing session, please register with Artair Mallett at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence all cell phones and all other electronic devices at this time.

Dr. Watson?

DR. WATSON: Thank you very much.

So we are ready to jump right into the meeting, and we are pleased to have a guest

speaker today. We have my friend Bob Ratner from the American Diabetes Association to speak to us.

Dr. Ratner?

DR. RATNER: Thank you, Madam Chairman.

My name is Robert Ratner. I'm Chief Scientific and Medical Officer for the American Diabetes Association, and I have no conflicts of interest. I was invited by the FDA to come present both the history and the current status of point-of-care hemoglobin A1c testing for the diagnosis of diabetes.

There are really two separate issues here. One is the utilization of hemoglobin A1c for diagnosis of diabetes, and the other is the specific use of point-of-care testing, hemoglobin A1c. So I'm going to start with A1c for diagnosis and then transition in the point-of-care component.

It's important to understand that the diagnosis of diabetes is a categorical diagnosis based upon a continuous variable. That always gives you potential problems. In 2010 the WHO concluded that A1c can be used as a diagnostic test for diabetes provided that stringent quality assurance tests are in place and that the assays are standardized, and perhaps even more importantly, that no other conditions are present which preclude its accurate measurement.

Now, when you begin to look -- I'm sorry -- when they made that judgment, the other component of this was that they judge the quality of evidence as moderate. Again, the assays that were available, the continuous nature of glucose, and the categorical nature of hemoglobin A1c was really the way that they were looking at it. And the strength of their recommendation was considered to be conditional.

Now, when you begin to look at how diabetes is diagnosed, historically, it's always been based on the occurrence and risk of retinopathy. So going back to large databases,

one could see the relationship between a fasting glucose level or a 2-hour post glucose load and the inflection point at which retinopathy started to go up.

All of these are squishy numbers, and I will grant you that right off the bat. Fasting plasma glucose is probably a more stable measure than the 2-hour post glucose load, but the 2-hour post glucose load is the most sensitive even though there are problems with replicability.

What you can see from this graphic from the NHANES data is that there are some arbitrary cutoffs on all of these values when retinopathy begins to go up. So one could say that 6.2 is the point at which A1c is elevated in the group that begins to develop retinopathy, and yet the set point is 6.5, lots of fluff around numbers.

When you begin to look at sensitivity and specificity of the hemoglobin A1c for diagnosis in different populations, you see a fairly large range. The specificity of hemoglobin A1c for diagnosis is fairly high. The sensitivity, on the other hand, depending upon the population that you're looking at, ranges from 47 to 60%. So there clearly are conditional issues related to A1c and diagnosis.

When you begin to look at special populations, children and adolescents with obesity, you can see from this data that fasting glucose is a better index for diagnosis than is the hemoglobin A1c.

And when you begin to get into ethnic populations, there clearly are differences. Here, you're simply looking at sensitivity for A1c in Arab populations, where you're getting down to the 15% range. This year at the Scientific Sessions of the American Diabetes Association, CGM data was presented in African Americans, Hispanics, and whites as it related to hemoglobin A1c, showing that the average glucose level in whites does not equate to the same average glucose level given the same A1c in African Americans. So there are conditions which clearly do alter the glycation of hemoglobin and the reflection

of ambient glucose. Here is simply another example within the Chinese population, where the sensitivity begins to come down. And in Chinese, even the specificity is reduced.

How does all of this relate to the American Diabetes Association? For the last 20 years, the American Diabetes Association has been annually updating its standards of care. These are evidence-based reviews of current literature getting to the clinical practice guidelines of what we really need to be doing for people with diabetes. All of our recommendations are evidence based. They do vary from expert opinion, where the quality of the data is limited, to A-level evidence based upon controlled clinical trials. Every recommendation has a grade associated with it.

So what's the history of where the ADA comes down on hemoglobin A1c and diagnosis and then ultimately point-of-care? In terms of diagnosis, the ADA went along with WHO in terms of recognition of the value of hemoglobin A1c for diagnosis. Clearly, there are some logistic advantages: A single blood draw regardless of time of day, regardless of fasting, clearly makes it a more convenient test. But the statement even in 2010 was that it's critically important to take age, race/ethnicity, anemia/hemoglobinopathies into consideration when using the test to diagnose diabetes.

Now, this is in a bit of a distinction from its use in chronic care, where the important component is not the categorical cutoff, but the intra-individual longitudinal response, where you're looking at the difference in an individual as opposed to where do you stand within a population.

So let's switch now from the concept of diagnostic value to point-of-care testing. And again, what the American Diabetes Association clearly identified was a value of point-of-care testing for hemoglobin A1c for timely decisions on therapy changes when needed. This is the intra-individual deltas over time and the index for a change of therapy.

The data here are really quite good. We have significant improvement in glycemic

control when point-of-care hemoglobin A1c testing is being utilized within a healthcare system. Multiple papers have shown this. It provides an opportunity for patient education, the ability to immediately during the visit interpret the hemoglobin A1c for the patient and use that as either a rationale for therapeutic change or a motivation for lifestyle modification. So there is no argument in our mind that there is value of point-of-care testing. However, we limit this not to the diagnosis but rather to the ongoing management of people with diabetes.

So when it comes to diagnosis, this is the recommendation from 2010. That was the year that we first recommended the use of hemoglobin A1c testing for diagnosis. But the exception here was point-of-care A1c assays were not sufficiently accurate at the time for diagnostic purposes.

Now, I mentioned that we review the literature on an annual basis, and every January we come up with updated standards of care. In 2012 we modified this particular recommendation to say that point-of-care A1c testing for which proficiency testing is not mandated are not sufficiently accurate at this time for diagnostic purposes, recognizing that the technology was improving, and with proficiency testing in ideal situations, that perhaps this could be of value.

In 2014 we became a little bit more dogmatic on this. Although point-of-care A1c assays may be certified, proficiency testing is not mandated for performing the test, so use of these assays for diagnostic purposes could be problematic and is not recommended.

In 2016 we've modified this a bit more. And again, the take-home message here is that point-of-care assays for diagnostic purposes are not recommended. Clearly, the value of point-of-care testing is for education and for therapeutic changes within an individual patient. Ideal situations for laboratory testing are necessary for labeling of individuals. At least reliable tests with proficiency testing become critically important in this regard.

There have been a lot of concerns regarding point-of-care A1c testing over time. Some of these have clearly been overcome by industry improvements. But outside of a laboratory situation where proficiency testing can be done and where controls can actually be looked at, there clearly are potential problems.

The labeling of a patient with diabetes has profound implications. It used to be that your insurance premiums went up. With the Affordable Care Act, that can't happen, but your life insurance premiums go up. Your ability to get a driver's license begins to change. And job discrimination clearly occurs. We need to be very cautious in who we label with the disease. And clearly, point-of-care A1c for diagnostic purposes has the potential of both false negatives and false positives.

The concerns here are lack of reproducibility and imprecision, the lot-to-lot variations in the reagents and the calibration, and in particular, the lack of proficiency testing at waived sites.

One of the concerns that the American Diabetes Association has is the widespread screening of individuals for diabetes in situations that really don't lend themselves to either patient education or patient care. And so, in 2016 our recommendations about community screening are shown here. Outside of the healthcare setting, it is not recommended to do diabetes screening because people with positive tests may not seek or have access to appropriate follow-up testing and care. Community testing may also be poorly targeted, both failing to reach the most at-risk populations and inappropriately testing those at very low risk or even those who have already been diagnosed. The idea of utilizing point-of-care hemoglobin A1c testing in a health fair is highly problematic from our standpoint, and we believe that opportunistic testing for diagnosis is the most appropriate approach.

We have worked with the CDC and the American Medical Association to increase

the visibility of diabetes and to encourage screening for diabetes and even pre-diabetes. But the settings and the circumstances in which that occurs is very specific. For many years, the American Diabetes Association has had a very simple risk test, paper risk test, several questions, all based on history, no physical exam, no laboratory tests required, which has a very high positive predictive value for the development of diabetes. This, individuals can take on their own on the web. We hand it out at all sorts of health fairs. But the instruction is if your score is greater than 5, see your healthcare provider. That's the circumstance in which the diagnosis can both be made and appropriate intervention can be provided.

So we are very concerned about the use of point-of-care A1c testing in community in which the follow-up is not assured, the sensitivity is low, the false positives may be present as well, particularly in certain ethnic populations. And so again, I return to our 2016 standards of care, which does not recommend point-of-care A1c assays for diagnostic purposes.

Thank you very much.

DR. WATSON: Thank you, Dr. Ratner.

I'd like to open up the question and answer period from the Panel. Do we have any questions for Dr. Ratner?

MS. McCOLLISTER-SLIPP: I have one. So understanding what you said about concerns about the accuracy of point-of-care and truly taking to heart the fact that this does have implications once that shows up on your electronic health record, especially because it's more difficult to get life insurance -- and I actually have a family member for whom that was an issue -- for community settings, like community screenings, as somebody who's done those kinds of things using blood glucose meters, I would think that the risk of discrimination might be less because it doesn't actually make it into your record

in most cases? It would just sort of be like this is something to be concerned about kind of a test. So it would seem to me that it could potentially be -- I think it would probably be more helpful than screenings with a blood glucose meter, which is what a lot of people do when they do diabetes screenings in these kinds of settings.

So I guess I'm trying to understand why you're concerned about that particular setting versus trying to drive people to a physician, which for a variety of reasons can be very difficult, especially for some of the vulnerable populations.

DR. RATNER: So there are several questions that are embedded in that. Community screening is problematic from the very beginning in our view, whether you're using glucose or hemoglobin A1c. In terms of the A1c, if you look at the sensitivity of 40 to 60%, what that's telling you is that you have an awful lot of false negatives. So you're providing reassurance to individuals who may, in fact, have the disease. And that false assurance may actually delay them going into a physician or healthcare system to receive appropriate care. So that's one concern.

The other concern is even with the true positives, when you're in a community screening setting, the question is what do you do with that information? Where do you go from there? What that's doing is it's setting up a system that doesn't serve the patient well because now they are told on the basis of a single test that they probably have diabetes, and again, the American Diabetes Association recommends two tests on separate days, and what is a person to do? So the anxiety level that that can induce is another potential problem.

If, in fact, the screening is taking place within the setting of a healthcare facility, that both alleviates the anxiety because you actually have clinicians there to explain the circumstance to them and to provide the appropriate follow-up -- let's confirm the test tomorrow or the day after; let's move on from here, and here's what we can do. I think

that labeling in a community setting and then letting folks go free is really the problem.

DR. WATSON: Yes?

DR. WYNE: So I also, because you raised the issue of community screening, had some questions very similar to Anna's. My understanding is, really, the strongest risk factor for type 2 diabetes is a family history of diabetes, which means a person knows they're at risk. They can go on the American Diabetes Association website, use the risk calculator, and confirm they're at risk. Then they can attend the community screening and get their finger pricked for a drop of blood.

My question is do you have any specific references showing me that there's going to be benefit of using an A1c in that setting, above and beyond a glucose level?

DR. RATNER: I have no data that shows a benefit of A1c over a glucose in that circumstances.

DR. WYNE: But that is a consideration when you're discussing community screening, because we've got a very good screening test that's already being used in that setting. I don't know the literature as well as I know personal experience, and what I hear from our educators, but what typically happens in a community screening is you tell the patient, the person, that their glucose is elevated. And the most common answer, yes, I know. I was curious how high I was today. And when you pursue it a little bit further, you can imagine -- you know, there's nothing from the community screening that forces medical intervention or facilitates, and as you clearly outlined, that's a problem.

I think in the health/wellness setting, there's a difference, because when it's an employer-related screening, there's often reinforcement, requirement, mandated activity. So you raised an interesting distinction between a screening in a health fair and a healthcare setting versus community. But I just thought it was interesting that within the whole issue, you raised the issue of community screening because I think that's one of the

most problematic places.

DR. RATNER: I completely agree with you. And again, to utilize systems with proficiency testing in ideal settings, the American Diabetes Association accepts the value of A1c for diagnosis. It's in the absence of point-of-care proficiency testing that we believe that the systems are problematic. So I have no disagreement with you at all.

MS. McCOLLISTER-SLIPP: So the issue -- and I mean putting aside some of the broader issues around community screening, so the issue is really that the tests just aren't that accurate yet for the point-of-care?

DR. RATNER: Again, the issue is differentiation between doing a test in an ideal setting with the appropriate controls and the appropriate technicians as opposed to a waived situation, where proficiency testing is not required and is not done.

DR. WATSON: Dr. Rej?

DR. REJ: Thank you for your presentation.

It seems from the current recommendation from the ADA and, I believe, the recommendation from 2014, that it's the lack of proficiency testing that is kind of the deal-breaker for the ADA.

What level of proficiency testing would you or the Society be comfortable with for such devices, and knowing that for medical laboratories under CLIA, proficiency testing typically only takes place three times a year?

DR. RATNER: I think that the difference between an established laboratory doing periodic proficiency testing is that you have stable technicians who are doing the tests in an environment that is unchanged.

The proficiency testing for point-of-care, I think, would probably vary according to the circumstances. If, in fact, it's a physician's office, where it's a single technician who's doing the test every day, that could probably be accomplished three times a year. If, on

the other hand, it's a Lions Club who's taking a machine that they bought down to the local mall, that's a different circumstance. And there, I think that quality control becomes a major problem.

MS. McCOLLISTER-SLIPP: So, again, as somebody who has done like diabetes screenings in these community settings, I mean, when I think about this -- and I also literally, as, you know, the diabetic that everybody knows, have had three different calls from three different people over the past month and a half who went to the doctor, had a high A1c test, and now they're like texting me to see if they can eat, you know, Chinese food or Indian like five times a day.

Putting that issue aside, I mean, these people were people who had access to insurance, they could go to the doctor, they could go back and get the repeat test, do fasting blood sugar, so they were very fortunate. I mean, I could see a case in which people not like that could potentially have access to these kinds of point-of-care tools of screening. I have no desire to give anybody a false negative, or a false positive for that matter, but I can see a utility knowing that none of us live in a perfect world, and many of us live in a far from perfect world. I could see the utility where this could be helpful. But again, maybe the issue is that it's just not as accurate at this point. I don't know. I'm sort of weighing the cost versus benefits of doing this versus not doing this.

DR. WATSON: So as I understand it, Dr. Ratner, it's the proficiency testing, as you said, Dr. Rej, which is the deal-breaker and that as long as -- I mean, I don't know that that is sort of something easily remediated since we don't know what all of the different factors are in every health screening, every community fair, everything, you know?

DR. RATNER: So the current CLIA regulations actually set it out fairly clearly. So if you have a moderately complex test, then proficiency testing is mandated. If you have a waived test, it may not be. So I'm not an expert in that. I think you have experts around

the table who can speak to that far better than I. It's a matter of how the test is ultimately identified in terms of the CLIA regulations.

Now, just to point out, there is concern about the proficiency testing for diagnosis. There is also the concern in terms of how and where it's going to be used.

DR. WATSON: Dr. Wyne?

DR. WYNE: I just have a quick question. You raise the issue of the impact of false positives. Is the ADA more concerned about false positives or false negatives?

DR. RATNER: We're concerned with both. The issue of false negatives is the sense of assurance that an individual may have when they really need to be speaking with a healthcare provider. The specificity historically has been pretty good with A1c. It's late to the diagnostic point, but when it's there, it's usually pretty good.

The biggest concern with the false positives is what we've seen recently in terms of ethnic differentiation. Whether it's fast glycators or there's something else going on is unclear, but at any given average glucose level, African Americans have higher hemoglobin A1cs. Are we going to start over-diagnosing in that population by utilizing the same cutoff point? It's impractical to have diagnostic cutoffs that are ethnic-specific. Defining ethnicity is hard enough, so we would never go in that direction. But there doesn't appear to be any differences in glucose by race and ethnicity.

DR. WATSON: Thank you.

Any further questions from the Panel?

(No response.)

DR. WATSON: Thank you so much, Dr. Ratner.

So I think now we are ready to move on to the Sponsor's presentation. Will the representative from Alere please approach the podium?

DR. SAN GEORGE: So good morning, everybody. I'd like to thank FDA and the Panel

members for giving us the opportunity to present to you today on behalf of Alere.

My name is Rick San George, and I'm the head of Clinical Affairs at Alere. We have an agenda set on the slide here today. We're going to talk about several things. We're going to give you a synopsis of our presentation, define some terms, give you an overview of the Alere Afinion Hemoglobin A1c Diagnostic Test. We're going to discuss clinical considerations, review some performance data, discuss laboratory director considerations, review the mitigations of potential sources of error, illustrate the distinction between moderate complexity tests and CLIA-waived tests that are in the market right now, and then summarize our presentation.

So in the way of synopsis and definitions -- sorry, I'm having a little trouble with the clicker. So the reason we're here today is because Alere has submitted a 510(k) application to obtain a diagnostic claim for the Afinion Hemoglobin A1c Dx product to aid in the diagnosis of diabetes and for use in clinical laboratories and moderate complexity point-of-care settings.

Okay. The potential benefits of point-of-care A1c for diagnostic use are significant while the potential risks are minimal. We're going to show you that the Afinion A1c diagnostic product is accurate, is precise, and it has a low total error. We're going to show you that as a moderate complexity point-of-care test, the Afinion A1c will be subject to all the same requirements for proficiency testing, quality control, and operator training as the already FDA-cleared A1c laboratory methods that are used for diagnosis. We're going to show that we have extensive and comprehensive error mitigations that have been incorporated into the design of the Afinion system to ensure accurate results in any setting, including CLIA waiver, and that our approach to ensure that CLIA-waived laboratories cannot use the new moderately complex test is a good one.

So this is just to define some terms, and probably everybody knows this already. I

won't spend a lot of time. But CLIA is the Clinical Laboratory Information Act. It sets the regulations for clinical laboratories. It classifies all laboratory tests into one of three categories.

High-complexity is in the right-hand column. These are the most complex tests. We're not going to discuss high-complexity tests today, but mass spectrometry, molecular diagnostics are examples of high-complexity tests.

In the middle column are the moderate-complexity tests. We are going to talk about those today. It is for moderate-complexity test that we have applied for a 510(k) with the FDA for using A1c for diagnosis. And you can see that proficiency testing is required for all moderate-complex tests regardless of where they're performed.

And we're also going to talk about the third class, the CLIA-waived class of tests. These are often performed at the point-of-care. Proficiency testing is not required. The educational requirements for the testing personnel are not specified, in contrast to moderate-complexity ones, where at least a high school education is required. And some examples of what the tests are: A1c for monitoring, as well as glucose meters and pregnancy tests.

I'm now going to give you an overview of the Afinion system. So, you know, in the earlier slides, I talked about the Afinion A1c Dx test, and that's the test that we've submitted now for that diagnostic claim. And it's been given a different name, because for the last 10 years, we've had a hemoglobin A1c test on the market to be used for monitoring glycemic control in people with diabetes. So that test is called the Afinion Hemoglobin A1c Test. It was cleared in 2005, and it was CLIA waived in 2006.

I want to mention that at the time that it was cleared and waived, it was done by a company called Axis-Shield in Oslo, Norway. They were the company that designed and developed the system and got the original clearances and waivers at these dates. And the

reason I tell you that is because Alere purchased Axis-Shield in 2011, but some of the data and some of the slides and some of the literature that you'll see later in this presentation refer to the Axis-Shield system, and I want you to know it's exactly the same system that we're talking about here.

Okay. So in other parts of the world, the Afinion A1c is legally marketed and widely used for both monitoring and diagnosis of diabetes, and some countries where this is being done are Norway, Sweden, and Germany.

Okay. The Alere A1c test offers lab quality, point-of-care, in-office results from 1½ µL of fingerstick or venous whole blood, and it's fully automated, simple, and safe to use, as I'll show you.

This is an illustration of the test cartridge, and some of the components are listed here. We were going to pass them around, and I'm not sure if we've done that yet, but in any case, I have a video that I want to show you that will illustrate the performance of a test.

Please?

(Video plays.)

DR. SAN GEORGE: So there's really three steps we're going to show you in this video, and it's very short. The first one is you just perform a fingerstick. You can see the operator here cleaning the finger with an alcohol wipe. They're going to dry the finger with gauze. They're going to prepare the lancet, press it to the finger, and do the puncture, create a small drop of capillary blood on the fingertip. They're going to collect the sample. There's a sample collection device that's part of the cartridge. You'll see it fills very rapidly and very easily, 1½ µL. The sample collection device is reinserted into the cartridge, and the cartridge is then inserted into the analyzer. The lid of the analyzer opens, the cartridge goes in -- there's only one way to put it in -- the operator closes the

lid, and the test starts.

During the test, there's a number of diagnostics that the analyzer goes through, both analyzing the cartridge for its integrity, reading the barcode on the cartridge for calibration information and for expiration dating.

Once all of that checks, the test begins. There's a progress bar that shows the progress of the reaction. The reaction takes about 3 minutes.

We'll zoom ahead to the end of the test. When the test is over, you'll see that the result is displayed. There it is. And when the operator presses that little check on the display on the touch screen, the lid opens, and the used cartridge can be removed and discarded. It's biohazardous waste. And it's really that simple.

Thank you.

Okay. So as we've just heard, in 2010 the ADA made a new recommendation for the use of hemoglobin A1c, and as FDA started to consider a test to be used for diagnosis, the following language was developed to describe the intended use.

So we'll just read this. It says, "Hemoglobin A1c measurements are used as an aid in the diagnosis of people with diabetes, as an aid to identify patients who may be at risk for developing diabetes, and for the monitoring of long-term blood glucose control in individuals with diabetes."

So the third of those intended uses is the one that's always been out there for monitoring glycemic control, and the first two, to diagnose and identify patients at risk, are the new uses for hemoglobin A1c. And as I've already told you, we've submitted a 510(k) for this intended use as a moderate-complexity test. And this test is called the Afinion Hemoglobin A1c Dx test.

And with that, I'd like to turn the presentation over to Dr. Richard Kahn, who will talk about clinical considerations.

DR. KAHN: Good morning. My name is Richard Kahn. I'm currently a Clinical Professor of Medicine at the University of North Carolina, having had that position for just a few years. Prior to that I was the Chief Scientific and Medical Officer for the American Diabetes Association for 25 years.

So I'm going to talk to you today, but before doing so on A1c and the Alere system, my disclosures are, of course, I'm a consultant for Alere, and also I'm an advisor to these three organizations. I have no other conflicts, potential conflicts of interest.

To give you an overview first of diabetes and diabetes testing, why we are gravitating more and more toward the A1c as the preferred test for diagnosing diabetes, and then I'd like to discuss a little bit why point-of-care systems are very important. And last is a concern of all of us, and that is the potential for false negatives and false positives and how can we mitigate against that.

So, first of all, testing for diabetes. There are millions of Americans, of course, as you all know, who are undiagnosed. The ADA estimates that about 8 million people currently have diabetes and are undiagnosed. Hyperglycemia, as you know, is a high-risk cardiovascular state, and that is really the problem that we're facing. We diagnose diabetes not to just diagnose diabetes but to prevent the long-term, chronic, serious complications of this disease. That's our primary emphasis in trying to treat diabetes.

We also know that hyperglycemia tends to worsen over time in all cases, whether it be type 1 or type 2 diabetes. Poorly controlled diabetes leads to serious complications. And finally, we want ideally a low-cost, rapid, convenient assay to diagnose diabetes.

There are, as we know, three assays to diagnose diabetes: the fasting plasma glucose, the oral glucose tolerance test, and now the A1c, as Dr. Ratner had pointed out. Each of these tests have advantages and disadvantages. A huge myth -- perhaps in my decades' worth of experience in diabetes, the greatest myth in all of diabetes is that there

is a gold standard test for measurement. And you can't have -- the concept of sensitivity and specificity rely on having a gold standard to which to compare it to. The truth is there is no gold standard for the measurement of diabetes, threshold for diabetes in which it indicates a greater proclivity for development of the long-term complications of the disease. So there really isn't a gold standard. That is a huge myth in the field.

The A1c test, as you can see from this slide, has enormous advantages. The first is that fasting is not required. Many people come into the office thinking they have fasted, but they have not. Many people don't tell the truth, that they had to have a little bit of something in the morning or in the afternoon to get by, and say they were fasting, but they have not. The A1c is independent of the fasting state. It has very low biological variability; in contrast, a measurement of glucose has high biological variability. It's stable under an acute illness; in contrast, measurement of glucose is instable in an acute illness. There's great sample stability in the vial; in contrast, glucose is relatively unstable in the vial. It can be measured any time of the day, the A1c; in contrast, the fasting glucose level is significantly higher in the morning than it is in the afternoon in people who claim that they've done an overnight fast. There's global standardization of A1c, much like there is in glucose. And finally and very importantly, it's directly related to management. We manage people with diabetes to avoid the serious complications of the disease, and we use the A1c test. That's the only test that's been linked to the development of the chronic complications of diabetes.

If we would look at a slide of fasting plasma glucose and oral glucose tolerance tests, virtually all of these advantages, with the exception of global standardization, would be disadvantages for all of the other tests.

There are disadvantages, as Dr. Ratner has correctly pointed out. It's very questionable in patients with hemoglobinopathy, certain anemias, advanced renal disease.

Fortunately, the Alere system obviates many of those points, and fortunately, the size of those populations are relatively small. Also, as Dr. Ratner correctly pointed out, there are racial and ethnic differences, and we just simply don't know what to do with them. We can't, at this point, change diagnostic thresholds. We don't know that. There's certainly overlap between the ethnicities. So there are differences, but we don't know really what they mean and what their impact are.

And it is now fast becoming the commonly used method to diagnose diabetes.

So ideally, again, we want a low-cost, rapid, easy, and accurate way to diagnose diabetes. And much like all of technology, whether it be computers, cell phones, TVs, calculators, airplanes, technology marches on, and things get better and better. As you've heard yesterday, things get better and better with technology. And I think we've reached the point, and I think you'll see in future presentations from Alere, that the Alere System is impressively accurate and precise, and it appears to be no different than virtually all central laboratory procedures. So point-of-care testing, I believe, meets these criteria.

In addition, it's efficient in many ways. To do point-of-care testing means that you don't have to call back the person. You don't have to have this person -- you don't have to ship the sample to an outside laboratory and deal with any kind of paperwork problems or any kind of handling problems with the sample. To have point-of-care testing is an enormous benefit in that regard.

It mitigates access-to-care issues, and many of the patients that we want to reach, they have difficulty coming back to an office the next day, getting away from work and coming to an appointment. Having a point-of-care test is a great advantage. It allows for the rapid initiation of treatment. You could at least initiate lifestyle modification therapy at the point-of-care and then retest, as we know from the ADA, which mandates retesting at some other point.

It capitalizes on a teachable moment. Here you have the person in the office, getting a test, found to have diabetes, and now you are right there. You can start to begin teaching the person about the impacts of the disease and what to do about it and plan the therapeutic regimen.

These benefits are the same as point-of-care monitoring, which are already approved. And to give you an example of what the impact has been of point-of-care monitoring, here are two studies shown in two graphs, two bar graphs. The one on the left shows what happened -- what was the frequency of monitoring, A1c monitoring before point-of-care testing was initiated and then after point-of-care was initiated. So point-of-care testing reduced the untested rate by nearly 85% in this study. This is for monitoring, not for diagnosis. That's important to remember. Point-of-care testing changed from 74% to 87% in this study. So point-of-care testing, which was made more efficient, actually led to people adopting it, as you would expect.

The same is true with this bar graph of all the studies I could find related to point-of-care testing and A1c lowering. And you see here, some of the slides marked in an asterisk, which are statistically significant, non-randomized studies, pre-test/post-test studies, or randomized controlled studies, point-of-care testing led to a reduction in A1c.

This is not an argument for point-of-care testing for diagnosis. It is an argument for if you make a test efficient and easy to use, people will do it, and there stands to be a good chance that there's going to be a benefit that results from it.

Okay. So now we talk about moving the thresholds and what are the considerations here. And we know that pre-diabetes has a threshold of 5.7 to 6.4. Diabetes is 6.5 and greater. And as Dr. Ratner pointed out, there is no magic at the threshold. Nothing. Mother nature doesn't work that way. These are manmade thresholds. And what we're concerned about, all of us are concerned about is this particular threshold of 6.5%.

The Alere System, false negatives, false positives, it's not going to happen with a person who tests an 8.5% in the Alere System and really is 5.2. That is not going to happen. Conversely, a person who is really 5.6 is not going to test 8.2. That's not going to happen. What we're talking about in false negatives and false positives with the Alere System is at around this cut point. So a test that comes out 6.6 might be 6.5 or 4 or 3. As you'll see from the next speaker and the next speaker and every which way you can cut the data, the Alere System, the precision and accuracy is such that if there's going to be false positives and false negatives, it's going to occur right around the cut point.

Okay. False negatives and false positives are going to occur just like they occur with every central laboratory procedures, every central laboratory procedure. Around this cut point, false negatives and false positives are going to occur.

How do we mitigate against this? The first, the ADA requires confirmation testing. That's a possible mitigation against the impact of a false positive. So you have an Alere System that's giving you a result of 6.6. You actually have a 6.4 or a 6.3. You actually do not have diabetes. So confirmation testing will mitigate against it. The person actually has high-risk pre-diabetes. What does high-risk pre-diabetes mean? Well, if you look at the very bottom row, with a level in this particular study, and in virtually all other studies, if you look at a level of 6 to 6.5, the 15-year risk for diabetes is enormous. These various models control for various factors. Regardless of how much you control for them, all the various variables that might be confounding, the risk for diabetes is enormous if you're in the 6 to 6.5, and that's where the false positive is going to actually occur in the Alere System.

Then, of course, the patient is subject to the consequences of treatment. They've been told they have diabetes, but they have high-risk pre-diabetes; they really have high-risk. So they're going to have visits, testing, and drug therapy. Well, what is that? Here

are the ADA recommendations for pre-diabetes and for diabetes. Both conditions -- and we're now talking about diabetes that's in the 6.5 to 6.8 category, in that range, not 8.2, not 9, so in terms of a false positive.

They both say, both conditions, intensive lifestyle counseling. Both conditions, more frequent follow-up. For pre-diabetes, it's at least once a year; for diabetes, it's two times or more a year. So it's slightly different. Both conditions, consider metformin for pre-diabetes, consider metformin for diabetes. Both conditions, screen and treat cardiovascular disease factors. Here, the goals of therapy for cardiovascular risk factors are identical with the exception of statins. Blood pressure goals are the same. If you have diabetes, basically you're automatically put on a statin. If you have pre-diabetes, you're not. So there are some differences, but it's not a huge change in therapy because you've crossed that threshold from high-risk pre-diabetes to diabetes.

Now, there's possible employment and insurance issues. Those are real. There's no question. You've been diagnosed with diabetes with a 6.7. You really have high-risk pre-diabetes, 6.4. There are possible employment issues. Mitigating against that, the Americans with Disability Act says you cannot deny or discriminate in employment. People still do, but the law says you should not. So it helps mitigate that factor. In the Affordable Care Act, it was pointed out you can't deny coverage, you can't charge higher rates, you cannot discriminate for a pre-existing condition, no dollar limits, etc. People slip through the cracks. It happens, okay? Those things happen, but there are mitigating factors for a false positive.

How about the psychological impact of diagnosis when you really didn't have that? In what I think is an exhaustive search of the literature, I could find no study that indicates the psychological impact of an immediate diagnosis of diabetes in terms of anything that follows long-term. There are many papers in the literature that say if you have diabetes

for 10 years, 15 years, 20 years, there is a psychological impact on that. But immediately upon diagnosis, I could not find one paper in the literature that addresses that.

But all of these points, it's important to keep in mind, either have the same -- you'll see -- the very same likelihood of a false positive as any or most central laboratory results. It's the same likelihood, the same consequences.

Let's turn around and look at false negative. Jeez. Now you've been told you haven't had diabetes, but you really do have it. You're, again, in that border somewhere. That's where it's going to occur, around the 6.5 range, that you really have a 6.3 -- oh, you have high-risk pre-diabetes, but you really have diabetes at 6.6 or .5 or .7.

So repeat testing, as mandated, will mitigate against that. The person will eventually find out they actually do have diabetes. The patient receives high-risk treatment, receives treatment for high-risk pre-diabetes when they should be getting treatment for diabetes. And again, the same slide. There's not a huge difference between the two. You have a high-risk pre-diabetes versus having been diagnosed with diabetes.

And the big question is, jeez, if you haven't been diagnosed with diabetes, are you more likely to get the chronic complications? So you're sailing along with high-risk pre-diabetes when you should be diagnosed with diabetes. What's your likelihood of chronic complications? To my knowledge, there are eight studies in the literature that address this issue of what kind of A1c does it take to develop the chronic complications of diabetes.

Here's data from one of those studies. All eight fundamentally show the same thing, and there's no other study that contradicts it. And that is, if you look at this bar graph on the left in this study, a Swedish study, these were people followed for 25 -- 20 to 25 years. If you didn't have an average A1c greater than 7.5, the risk of developing retinopathy was virtually nil. On the right side, if you didn't have an A1c greater than 7.6,

the risk of developing macroalbuminuria was virtually nil.

In all the studies, the magic threshold, so to speak, appears to be 7% or greater for a long period of time. Here's another study that -- this is from an American ADVANCE study. Patients were followed for 10 years. And this study shows that macrovascular events, if you had an average A1c below 7, they didn't happen, relative to the control group, no diabetes. It didn't happen. If you had an A1c less than 7%, all-cause death was the same. For microvascular, they made the cutoff 6.5 or higher, so we don't know for microvascular disease what the case is, but we do know from the previous study. So, again, 7% for a long period of time appears to be the threshold to do the follow-up on complications to diabetes.

So here's this person who has diabetes, 6.5, 6.6, 6.7. They're not going to get the complications of diabetes because they're going to be picked up within a year or two or even three. And the progression, the worsening of diabetes from the two studies we have data on indicates that progression is about a little bit less than 0.1% per year. A little bit less than 0.1% per year is the average worsening of diabetes from the only two studies from which we have data in that regard. So the likelihood is very, very slim that the false positive -- or false negative, false negative that we're talking about, that an individual is going to develop any serious complications before being picked up and diagnosed with the disease.

Again, these false negatives, as you will see, have the very same likelihood as any central laboratory test. It's not going to be any different. Technology marches on. It's getting much better.

What's the impact of all this? If you look at the circle on the left, okay, you have how many people in the American population meet the criteria for A1c testing, or for testing for diabetes? Seventy-one percent, 142 million. Of these people right here, of the

142 million, how many of them were tested for diabetes? Forty percent were not tested in the previous 3 years, okay? These are people who meet the criteria for testing, have not been tested.

Of these who have not been tested in the last few years, how many of them -- this is based on NHANES data -- how many of them actually have visited their healthcare provider? Eighty-four percent, which means that of these, 1.4 million of the 8 million people with undiagnosed diabetes -- that's the potentially low-hanging fruit -- they could be tested with point-of-care testing. And if we believe that the efficiency of testing will go up when there's a point-of-care device, in fact, we stand a great likelihood of reaching these people and diagnosing the disease.

So, in conclusion, the potential benefits of point-of-care A1c testing are significant while the potential risks are minimal. And I'll add the potential risks, as you will see, are no different than already approved central laboratory procedures.

DR. WATSON: Thank you.

DR. SAN GEORGE: Speaker --

DR. WATSON: Yes. Continue with the Sponsor's presentation.

DR. SAN GEORGE: Yes. Thank you, Dr. Kahn. This is Rick San George speaking again.

I'm now going to briefly summarize some of the performance data for the Afinion A1c Dx test.

You know, we've heard a lot of general concerns about point-of-care A1c use for diagnosis. We've heard concerns that it's not accurate enough. We've heard concerns that it's not precise enough, that it lacks reproducibility. We've heard concerns that there's a lack of mandated proficiency testing. We've heard that there are lot-to-lot variations in reagents and calibration. We've heard there's a lack of ongoing quality

assurance of the results. And finally, there's unknown performance in CLIA-waived settings. What I'd like to do now is show you that these concerns do not apply to the Alere Afinion A1c Dx test.

And before I do that, I just want to acknowledge that FDA had stated in its Executive Summary that they want the discussion at this Panel meeting to focus on the questions related to POC use in CLIA waiver, and we concur with that focus for this meeting. FDA requested that for the purposes of this discussion, the Panel assume that the Afinion Dx assay has equivalent analytical performance to other cleared diagnostic A1c tests, and we're glad to see that assumption made. What we'd like to do is actually demonstrate why we believe that is a good assumption. And the reason for that is because, as we just showed you and as you've heard already, most of the concerns around point-of-care testing are centered around performance, especially in terms of accuracy and precision and the risk of an erroneous result.

And so, with that, I'd like to show you a little bit of the data. These are the FDA special controls that manufacturers must meet in order to submit data for consideration for a diagnostic claim for the use of A1c. The first one says that the method has to be standardized and certified to be standardized. And I can tell you that we have NGSP certification for the Afinion system. NGSP is the National Glycohemoglobin Standardization Program. We've certified that system, the Afinion system, really for the last several years. And as the requirements for certification have gotten tighter with the diagnostic claim, we've certified it to those tighter specifications, as well.

The second point is all about analytical performance, and there are three sub-points related to precision, accuracy, and requirement that the total error be less than or equal to 6%. I'm going to talk a little bit about each of these. But the special controls define how these things need to be assessed and what kind of performance needs to be

seen.

The third one is about interferences from hemoglobin variants. I'm not going to talk about that, although there are data in the Executive Summary if you want to see that or if you want to discuss that. I can just tell you that the Afinion method is based on a technology called boronate affinity. And that method, in general, is less sensitive to interferences from hemoglobin variants than some other immunoassays or HPLC methods.

And so if we look at performance, we have to calculate something called total error, and total error combines error from inaccuracy and from imprecision. And the equation by which it's calculated -- sorry -- equation by which it's calculated is shown here. You calculate something called the percent total error. It has elements of percent bias. That's inaccuracy. That term appears twice in the equation. It has elements of imprecision. That's given by the percent CV, or coefficient of variation. And the percent total error is calculated as shown.

We perform an accuracy study per the specifications provided by FDA, and we determine the percent bias. We perform precision studies also per the guidance and specifications of FDA and obtain the percent CV. We combine them, as calculated above, to get the total error.

So in the accuracy study, here are the results. And there's a lot here, so let me just take you through them quickly. If we look at the scatter plot on the right, you'll see what we're doing is plotting the Afinion A1c Dx test results on fingerstick whole blood samples. This slide is for fingerstick whole blood samples, and we're comparing them to the Tosoh G8 method. This is the secondary reference laboratory method. It's performed at the University of Missouri at the NGSP laboratory under the direction of Dr. Randie Little, who's the head of the NGSP program.

And the scatter plot shows the data. It shows an identity line, dashed; it shows a

regression line, solid line; and it shows -- hard to see -- a dotted line with the plus or minus 6% limits for total error.

And the regression line is shown here. You can see that the slope, 0.997, is practically 1. The intercept 000 is, in fact, 0 in this case. The correlation coefficient R is very high at 0.991. There were 120 samples in this particular comparison. I can also tell you that in the accuracy study, 97½ percent of the results were found to be within the plus or minus 6% total error limits. To get NGSP certification, you need 37 out of 40, or 92½ percent within plus or minus 6%. So, in fact, this is very good performance.

If you calculate the percent bias at different levels of hemoglobin A1c, if we look at the decision level of 6½, the bias is -02 units of hemoglobin A1c. What that means is if the true value is 6.5, the Afinion gives, on average, a value of 6.48, practically no bias, practically no inaccuracy. And on a percent basis, that's 0.3% and -0.3%, well less than 1%. And you can look at the biases and the percent biases at the other levels, and they're all about 0.3%.

So the conclusion from this is that the Afinion A1c Dx test is accurate on fingerstick samples.

You know, three lots of cartridges were used in this particular evaluation. This shows the results for each of the three lots. What you can see is that they're all the same. The slopes and intercepts are practically 1 and 0 in every case. The conclusion is there's no significant lot-to-lot variability on fingerstick samples.

If we look at venous whole blood, the story is pretty much the same. The scatter plot on the right shows the results on the Afinion using venous whole blood versus the Tosoh G8, run at the NGSP lab. You can see the regression line again as a slope close to 1, intercept close to 0, very high correlation coefficient, and 97.1% of the results were within plus or minus 6%. The bias at the decision level of 6.5 is practically 0, and you can see the

percent biases are well less than 1%.

Again, on venous whole blood, we conclude the A1c Dx test is accurate.

And the same story if you look at lot-to-lot. Three lots used in the study. The regression lines are very similar. Slopes and intercepts close to 1 and 0, respectively, for all three lots. There's no significant lot-to-lot variability is the conclusion.

What about precision? So in that accuracy study, we do two fingersticks on every patient who participates. And we can measure the difference between those two. We can calculate something called the standard deviation of the duplicates. And we can pool those duplicates over -- many duplicate pairs. We pool them in different concentration intervals of clinical interest. So you can see we've pooled the values, samples between 4 and 6, 6 and 7, and 7 to 10. You usually want a significant number of duplicate pairs to do this analysis. Thirty is a good number. So with these intervals that we've selected, we have 47, 68, and 51 for those first three intervals. The 6 is really not very many for the interval greater than 10. You calculate those duplicates, standard deviation divided by the interval mean to get the duplicate percent CV. That's in the right column here. And you can see the CVs are all less than 2%. You know, in the region of 6 to 7 where the diagnostic cutoff lies, the percent CV is actually 1.4%.

So let me just make a little bit of comment. You know, these are really good CVs for a fingerstick assay, and there have been concerns expressed about fingerstick assays. We know in glucose, for example, there are sometimes difficulties getting precise measurements of glucose on fingerstick samples. Interstitial fluid is a common interferent.

It's important to note in the measurement of hemoglobin A1c that we're measuring a ratio of two things. We're measuring the glycohemoglobin, and we're measuring the total hemoglobin, and we're taking a ratio of those two. So if there's a little extra sample, the glyco is elevated, the total is elevated, the proportion is the same. If there's a little

less sample, there's a little less glyco, there's a little less total, the proportion is the same, the percent is the same. And so if there's dilution by interstitial fluid, it doesn't impact the measurement. It means that the glyco is diluted a little bit, it means the total hemoglobin is diluted a little bit, and the proportion is the same.

And there are several other reasons why precision on A1c -- it's a red blood cell test. It's not a plasma test. There's several other reasons why precision, and accuracy for that matter, on A1c can be achieved that are not able or easily achieved by other methods, like glucose, for example.

So the conclusion here is that Afinion A1c test is precise. We see less than 2% CVs on fingerstick samples.

If we look at venous whole blood, we can evaluate precision on venous whole blood samples in a more traditional way. These are also -- excuse me -- these values are also obtained per the guidance from the FDA. There are four levels of hemoglobin A1c that were selected: fresh venous whole blood samples at low, threshold, medium, and high levels. These were obtained at three different sites with three different lots with -- there's a large *n* in all of this, 80 replicates per sample, three lots, three sites, 720 measurements in all of these, two control levels. You can calculate in the standard way the percent CV and get the total CV, which is in the right-hand column. And again, we see CVs that are less than 1.45% at all levels, in some cases less than 1%.

So the conclusion is the Afinion A1c Dx test is precise. The CVs are less than 1½ percent on venous whole blood samples.

So now we can calculate total error. We have estimates of percent bias, as I've shown you from the accuracy studies. We have estimates of percent CV from the precision studies. We combine them per that equation I showed you earlier. And we get total errors shown in the right-hand column here. If we focus the decision level for fingerstick

whole blood, the total error is 3.07%. For venous whole blood, it's 2.53%. You can see at any level for any sample type, the total error is no higher than 4.1% in these particular studies. And in all cases, it's well less than the 6% allowable total error that was considered acceptable. So, you know, there's the equation again at the bottom of the screen, and the total error for both sample types at all levels is less than 4.1% based on these data.

So I just want to put this in a little bit of context. There have been several methods, laboratory methods that have been cleared for -- several laboratory A1c methods that have been cleared for use in the diagnosis of diabetes. You can look at the 510(k) decision summaries for these assays. It's publicly available at the FDA website. And we can look at those total errors compared to what we've just seen for the Afinion.

And I want to point out -- and you know, FDA wants to be sure that everybody knows that the Afinion have not been fully reviewed by the FDA. To that extent, then, the performance characteristics for the Afinion A1c Dx assay have not been fully established. The data presented here are not from head-to-head studies, and they are not intended to imply superiority. But the reason I want to show them is because, again, we've heard so many concerns about the accuracy of point-of-care methods. And maybe those concerns are legitimate, but they don't seem to apply to the Afinion A1c method.

Okay. These total errors, what I'm showing here are Afinion fingerstick by the maroon bar here and for venous whole blood down below. And you can see what the range of total errors are for those other assays that have been cleared. They're all well less than 6%, but so is the Afinion. And these are the data from -- at the cutoff of 6½ percent A1c.

And if we look at the other levels of A1c, this is for 5%, you can see that the Afinion total errors compare favorably with laboratory methods that have been cleared for

diagnosis. And if you look at the higher level of A1c, 8%, you can also see that the Afinion compares favorably with the laboratory methods that have been cleared for diagnosis.

Same disclaimers here.

Okay. What about the concern regarding assurance of ongoing quality? Well, two levels of quality control material are available for the Alere Afinion A1c. CLIA regulations, as we already heard, require for all moderate-complexity tests that two levels of QC material be run daily or an alternative IQCP plan be implemented. And this is true for all moderate-complexity tests regardless of where they're performed, whether it's POC or central laboratory. So that concern should -- does not apply in a moderate-complexity setting where this system would be used.

What about proficiency testing, concerns about lack of proficiency testing? Well, we know the CLIA regs require moderate-complexity tests and labs performing them to participate in CMS-accredited PT programs. It involves purchasing samples, three to five fresh whole blood samples, two to three times a year. The assigned value is not known. The laboratory runs them, reports them to the provider. Often that provider is CAP, College of American Pathologists. The laboratory receives back the results and sees how they are performing. And again, this is true for moderate-complexity tests regardless of where they are performed, whether POC or central lab. So Afinion A1c Dx test in a moderate-complexity lab is subject to the same proficiency test requirements as any other moderate complexity test, lab or otherwise. So the lack of proficiency testing here doesn't apply, or the concern about that does not apply.

Okay. So, to summarize the performance, you know, what we've shown is that the Alere A1c test is accurate, it's precise, it exhibits insignificant lot-to-lot variation, it exhibits a total error less than 6%, as required by FDA special controls.

Okay. We'd like to make the point that each hemoglobin A1c test should be

evaluated on the merits of its own performance and not where it is performed. And we want to just reemphasize the requirements for a moderate-complexity point-of-care A1c test or laboratory test are the same. The same PT requirements exist, the same requirements for QC apply, and the same operator training is required and applied.

So, to that extent, going back to where I started with some of this, if we look at the concerns that I mentioned earlier, the concern that it was not accurate enough, I think we've shown it doesn't apply to the Afinion here. The concerns that it's not precise enough, I think we've shown it doesn't apply. The concern about lot-to-lot variations, I think we've shown it doesn't apply. The concerns about lack of mandated PT doesn't apply in the moderate-complexity setting. Lack of ongoing quality assurance doesn't apply in the moderate-complexity setting.

Unknown performance in CLIA-waived settings, we haven't addressed that yet, but that's going to be the subject of some of the remainder of this presentation. So we will talk about exactly that coming forward. We'll talk about the mitigations of potential sources of error that are built into the Afinion system, and we'll outline our proposal for making the distinction between the moderate complexity for diagnosis that we're applying for and the distinction from the existing CLIA-waived tests for monitoring.

And with that, I'd like to turn the presentation over to Dr. Mitch Scott. Dr. Scott is a former AACC president. That's the American Association for Clinical Chemistry, and he's currently an associate editor for *Clinical Chemistry*, which is that organization's primary journal.

Dr. Scott?

DR. SCOTT: Thank you, Rick.

My name is Mitch Scott, and I am a professor of pathology and Medical Director of Chemistry and Point of Care Testing at Barnes-Jewish Hospital, Washington University

School of Medicine.

My disclosures. Obviously, I'm a consultant for Alere, also for IL and Becton-Dickinson. I receive research support from Siemens, Abbott, and IL.

Okay. I was asked to look at the questions being given to the Panel and think about those from a perspective of a laboratory director and what thought process I would go through implementing a new test in terms of its performance, any risks that are associated with the use of that test. And really what I would do and what I'll describe to you is the same for whether it's a point-of-care test or whether it's in my main central laboratory.

And these concerns for any test begin with the analytic performance. And what I'll do is I'll go through some proficiency testing data, the peer-reviewed literature. I'll look at some studies where the Afinion is used in a physician office setting, and then I'll briefly mention the 510(k) data that we just saw. I would go through all of these steps in addition to in-house validation of any new test being brought into my laboratory.

When you have these arbitrary cut points -- if it's black, you have diabetes; white, you do not have diabetes -- we have to consider the probability of a false positive or a false negative. And I'll give you a very simplified calculation given a total error of 6%, which is the requirements of the FDA and NGSP, of what that would be.

And then, finally, I was asked -- and this is in regards to Question 3 -- what about the risks involved in a waived setting. And there is when you start to go think about what could possibly go wrong outside of the central laboratory.

Okay. I just want to remind you that this submission is for moderate-complexity use, which means that if cleared, end users would have to participate in proficiency testing and do daily QC, just as any other moderate-complexity test.

All right. Let's talk about the analytic performance from proficiency testing data and from the literature of the Afinion system. So every CAP, College of American

Pathologists, proficiency testing cycle, there are between 50 and 80 users of the Afinion A1c test that participate. Very few, if any of these, are likely to be small -- whoops -- okay, it's not going back -- there we go. Few, if any of these, are likely to be GP, small physician offices. They are using the Afinion in a waived setting and do not have to participate in PT.

These 50 to 80 sites that participate in CAP proficiency testing are most likely -- and they are certainly in the case of our institution, where we use a point-of-care method called the DCA. These are large centers with point-of-care A1c in their diabetes clinics, their medicine clinics that are running under CAP certification and are under the auspices of the central laboratory. So our point-of-care testing for A1c is under the central laboratory direction. So we participate. It's essentially a moderately complex environment.

And the Alere Afinion has been NGSP certified since 2005. The current criteria of NGSP is plus or minus 6% relative total error for 37 of 40 samples, which is a pass rate of 92½ percent.

Okay. I'm going to spend a little bit of time on the first one, because this is -- these next four slides are fairly busy. These are from the NGSP website. And it summarizes the performance of all of the different methods. So on the *x*-axis are all of the different methods for A1c that participate in CAP proficiency testing program. You will see on the right are several central lab methods from Abbott. About a third of the way to the right are some HPLC methods from Bio-Rad. In the middle are a bunch of central lab methods from Roche. There are some Siemens methods. And indicated by the arrow is the Afinion Test. And you'll see in this particular CAP/NGSP sample, which has a NGSP-assigned value of 5.3, little bias and good between-site imprecision. So you're looking at the two standard deviation range of values from all 57 sites here. And it's very comparable to all of the central laboratory methods that are listed here. And there is another point-of-care

method listed here, which is the DCA from Siemens.

Okay. Now, I've just chosen four examples as close to the cut points as the CAP values had, and I'm going to go through the next three fairly quickly. So this one is from the first cycle in 2016. Here's one from the last cycle of 2015, with an assigned value 5.9%. The arrow again indicates the Afinion performance. In this case, no bias and good imprecision between laboratories, similar to or better than some of the central laboratory methods. Here's one from 2015, near the cutoff, 6.8% in this case. Again, little bias, good imprecision between laboratories for the Afinion. And the last one I'm going to show you is from 2014, and it has a value of 6.6%, again, very similar performance to the central laboratory methods.

Okay. Another thing that I would do with any new test coming into the lab is I would review the literature. And what I'm going to show you are several studies that have very large *n*'s, and they are from very well-respected groups.

The first study is from Robbert Slingerland's group. And Robbert is part of the IFCC hemoglobin A1c standardization group. He oversees that along with Cas Weykamp. And in this study, which Dr. Ratner actually alluded to, they did a full-blown CLSI. The lab people know what that means, but it's the Clinical Laboratory Standards Institute. They did an EP-9, full-blown protocols for precision, accuracy, and bias. They looked at eight point-of-care hemoglobin A1c methods. And the comparator that they used was the mean of three secondary reference methods. These were an immunoassay from Roche, a boronate affinity assay from Primus, and the Tosoh HPLC. The means of those reference methods was used as the comparator.

Here, you see imprecision data in red from Afinion, as well as some of the other point-of-care devices, and you'll see that the imprecision of the Afinion method -- and this is a full EP-10 evaluation -- is less than 2½ percent at the various levels tested.

Here is a scatter plot of the Afinion versus the comparator, and two different lots. The dark circles are Lot 1, open squares are Lot 2. You do see above values of 10 that Lot 2 started to introduce a little bit of negative bias. Remember, this was in 2010.

The authors' conclusion at that time was that only the DCA Vantage and the Alere Afinion methods met the current NGSP accuracy and precision criteria. So in this full-blown evaluation in a well-respected laboratory, the Afinion met the NGSP criteria at that time. Now, note, I think studies like this -- remember, only two of eight fulfilled requirements -- are the root of the ADA hesitancy about using point-of-care A1c methods. At this time, some of the point-of-care A1c methods, quite frankly, were terrible, and there would be concern about using them.

So the same authors repeated the study in 2014. They were now using the new tighter and current NGSP criteria of plus or minus 6% total relative error and 2% CV. Again, there in the red is the Afinion imprecision data, all CVs less than 2.1%.

Here's a scatter plot again, the two lots which show very good agreement here. And 97% of the values were within the NGSP criteria for acceptable accuracy. The authors' conclusion: The Alere Afinion, the DCA Vantage again, and a Roche method not available in the U.S. met NGSP criteria for accuracy and precision.

Okay. These studies, as well as the 510(k) data that you saw earlier, were done in a well-controlled laboratory setting. What about physician office settings? Those participating in the PT, as I said earlier, are most likely academic center clinics under laboratory control. So what about point-of-care testing for A1c in a GP, general practitioner, setting?

This study is from the U.S. and with 700 subjects from seven pediatric diabetes clinics. The comparator was the Tosoh HPLC at the University of Minnesota. Precision was done using six NGSP samples at three of the sites. Important to note is that the testing

here was performed by nurses in the diabetes clinics.

Here, you see the imprecision of the Afinion again in the red box, all CVs less than 3% at the diagnostic cutoff, and around the diagnostic cutoff, percent CVs were 2. Here is the accuracy compared to HPLC, and the scatter plot clearly shows good agreement to the secondary reference method performed at the University of Minnesota. So the author conclusions here were that both the DCA and the Alere Afinion have acceptable performance for routine use in pediatric clinic settings, that the differences to HPLC were clinically insignificant.

Okay. Another study in a GP setting was published by Sverre Sandberg. And I have to say a few words about Sverre. He is an internationally recognized expert in proficiency testing and point-of-care testing. He runs the Norwegian NOKLUS EQA program. EQA stands for external quality assurance. It's another term for proficiency testing.

This study looked at 1,288 general practitioner offices who participated in the NOKLUS program in Norway and 52 hospital laboratories in Norway. Acceptable criteria were the same as the NGSP. And this is what -- a summary of that data focusing on the Afinion and the central laboratories.

So the number of Afinion participants by the end of this 6-year period, 2006 to 2012, was around 600 of the 1,288 GP sites. And what you see in the red line is the percent of sites using the Afinion that fulfilled all of the NGSP criteria. And you see it bounces a little bit year to year, cycle to cycle, but on average, it's around 70% of the sites fulfilled all of the NGSP criteria in a GP office setting. The blue line shows the percent of central laboratory methods that fulfilled all the NGSP criteria. And again, there's some bounce year to year. But it averages around 70%, as well. So the fulfillment of NGSP criteria of the Afinion is absolutely identical to that of the central laboratory. And I should say that in Norway, there are minimum education requirements for those performing

point-of-care testing. They are called health secretaries, and the educational requirement is 3 years of high school, whereas we have for waived site, no educational requirements. Norway requires 3 years of high school.

Dr. Sandberg's conclusion was that a large percentage of GP offices using the Alere Afinion -- again, you see the DCA -- meet acceptable performance criteria and that GP offices for these two methods are similar to central labs.

Okay. How about some other proficiency testing data where GP offices are actually participating? Now, in Switzerland, PT testing for GP offices is required. In Switzerland, the education requirements for those performing proficiency testing are the same as the U.S. There are none. So I'm going to show you data from that proficiency program in Switzerland and one from Sweden, where we have 754 GP offices, 268 of which use the Afinion. In Sweden, the educational requirements for those performing testing are a high school degree plus one-year training as a nurse assistant.

So the Switzerland data. Again, the red box shows the Afinion at 99% of sites for sample A and again 99% of sites for sample B fulfilled their requirements for accuracy.

In Sweden, again, here, the Afinion *n* is 268 GP offices. The between-site CV was 2.6%. There's virtually no bias from the target value, and the target value is assigned by the IFCC standardization group. And you see other lab and point-of-care methods. The point here is that in a GP office setting, the Afinion performed equally as well as the laboratory methods participating in this Swedish program.

Okay. We've seen the 510(k) data. I'm not going to go through it, but it's consistent with what I've just shown you, that the method is accurate and precise.

All right. What's the probability of a false positive? And we're just going to make a few assumptions here so that this calculation is simple. One is that the A1c method has a total error of 6%, which is the NGSP requirement. We're going to assume that most of the

total error is imprecision with little bias, which we have seen for the Afinion. And we're going to say that my true A1c is 6.1, so high-risk pre-diabetes but not diabetes. What's the chance that I'm going to be diagnosed with diabetes? And again, we're assuming that the error is normally distributed in this simple approach.

So 6% of 6.1 is 0.36. We'll round that to 0.4. There's a 5% chance that my value will fall outside of that plus or minus 0.4 range or 5.7 to 6.5. Here, for a false positive, we're only concerned with the right side of the distribution. So there's a 2½ percent chance that my A1c will be greater than 6.5. However, according to ADA guidelines, you have to have this value confirmed. So the chance of the second value being greater than 6.5 is also 2.5%, if we disregard any biological causes for the false positive. And 0.025 times 0.025 is 0.000625, or 0.0625%, and that's 6 out of 10,000. So 10,000 people with a value of 6.1 will actually generate a 6.5 in a method that has a total error of 6%.

Okay. I'm going to end with thinking about Question 3, using this in a waived setting. Maybe the Norway, Switzerland, Swedish GP offices are a little better controlled than U.S. GP offices. I don't know. But what could happen? You could have a bad instrument calibration, a bad cartridge, a bad sample, although Rick already addressed the fact that we're measuring a ratio, not a concentration. So sample volume is not as big of an issue as it is with other tests where you measure a concentration. The cartridge could be damaged. It could be dirty. You could stick it in wrong -- well, I know you can't do that because I tried. And the next presenter will go into detail of all the mitigating steps that address each of these concerns that I as a laboratory director would be concerned with.

So my conclusions are that the analytic performance of the A1c is indisputable in a laboratory setting. The waived studies have not been done, but based on the mitigating steps that Alere has showed me, the analytic performance, my prediction would be that my response to Question 3 would actually be I would not have very many concerns.

We use the DCA, as I said, in a point-of-care setting and are comfortable with it for all of the above reasons that I've described for the Afinion. And our clinicians greatly appreciate the rapid access to A1c results and the teachable moments that it provides.

Thank you. And I'm going to turn it over to Frank, who's going to talk about all of the mitigating approaches used in the Afinion device.

DR. FRANTZEN: Thank you, Dr. Scott. My name is Frank Frantzen. I'm heading R&D at Alere Technologies in Oslo, Norway, the company that has developed the Afinion system and also where new developments of tests are being performed. I will in this first section of my presentation talk about mitigation of potential sources of error.

So what could go wrong in A1c testing in a point-of-care setting? Analyzer malfunction is of course a concern, the same with lot-to-lot variation, assay processing errors that could occur when the cartridge is being processed in the analyzer, and then we have the group of user errors, everything from incorrect cartridge storage conditions, compromised sample, incorrect operating conditions, and incorrect user operation. I will address each and every of these and the mitigating steps preventing Afinion from giving out erroneous results as a result of these potential sources of error.

To address mitigations against analyzer malfunction, all instruments have a fixed factory calibration. It's not possible for the operator to intervene or change this. In addition, there is a comprehensive quality control testing scheme going on and being performed on each and every instrument being released. This means that an instrument being released today shares exactly the same performance and quality as the instrument being released 10 years ago. And proving the effect of these mitigations is the fact that there has been no drift in analyzer calibration and no medical device reports associated with an erroneous result arising from compromised Afinion instruments in its 10 years in the market field.

Further, when it comes to mitigation of analyzer malfunction, the analyzer will start a self-test immediately after you turn on the instrument. And this is to test vital parts of the instrument and to secure that it's up to standard when it's being used. There is a series of tests being performed. I will not go into the details of each of them, but we can discuss that if someone is interested afterwards. The thing is that if any of these fail, the instrument would render itself inoperable so it cannot be used and it cannot be used to run samples. This self-test is performed every time you turn on the instrument, but if the instrument is left idle for more than 24 hours, it will actually start by itself every 24. So this is to secure that the instrument is performing according to its standards.

Lot-to-lot variation, how do we mitigate this? The lot-specific calibration information is stored in the barcode of the cartridge. Each test lot is calibrated against an internal reference lot, and stringent procedures are in place to secure that this internal reference lot is aligned with the NGSP reference. This has been done through collaboration with the IFCC network labs that do have bimonthly monitoring. We do, in fact, receive fresh IFCC-certified samples every second month. We have NGSP and IFCC certification. We participate and monitor external quality assurance surveillance programs.

What could go wrong during the assay processing, and what are the mitigating steps? The Alere Afinion A1c Dx test is continuously being monitored within the analyzer during sample processing. We have seen the video, and before the analyzer started the processing of the sample, there was a check sequence. And in this check sequence, every vital -- sorry -- every vital part of the cartridge is being checked before the assay is being started. So the geometry of the cartridge to look for deformities, if something is defect. The sample device is being checked. The sample is being checked that is present in the capillary, everything, and every function of -- from the cartridge that could affect the

analytical result is being tested before the assay is started.

And then the assay, during the whole processing time, is being followed by a range of different sensors being there in order to secure that the assay is being performed at its optimal rate. These sensors have a dual function. First of all, they sense everything from temperature, pressure control of the pumps, there are timing functions there, and the camera follows each and every movement and transfer step that is handling the cartridge. This is also being fed into the software so that the software can perform the analysis in the best possible way. However, if any of these sensors detect deviations outside specifications, the assay will be aborted. They will not be given an analytical result but instead an information code. And this information code makes the operator able to understand and identify what went wrong.

Over to operator errors. What about incorrect cartridge storage condition? How can this be mitigated? First of all, the labeling clearly instructs the user about the storage temperatures and also duration. And in case the operator actually uses an expired cartridge, this will be detected by the camera in the instrument via the barcode, and the cartridge will be aborted. In the same way, when it comes to an incorrectly stored cartridge, if any of the volumes, for instance, of the reagent in the cartridge has been altered due to elevated temperature or something, this will be checked before the assay is started. And if outside specification, the instrument will abort the assay and inform the operator through an information code about the error that happened. And after all, Alere has also as a safety buffer validated storage conditions that exceeds those stated in the labeling. This relates both to room temperature storage and also to storage in the fridge in combination with several freeze/thaw cycles.

Okay. The sample. The sample is a potential source of error, and also sampling. And I will repeat again, the Afinion Dx measures a ratio of glycated hemoglobin to total

hemoglobin, so the test is not sensitive to sample volume variations. It is not sensitive to dilution by interstitial fluid. And the typical problems with other fingerstick assays, such as glucose, like difference in oxygen tension between capillary and venous blood, differences between sample matrices, and the use of anticoagulants or not also do not apply to the test.

Still, there could be that a compromised sample is being used. And a compromised sample could be -- sorry -- a compromised sample could be a hemolyzed sample. If the hemolysis is moderate, this will not interfere and cause any error reports or information codes or abortion of the assay. However, if the hemolysis is large, this will be detected by the analyzer. The test will be aborted because this could compromise the analytical result, and an information code is provided. And after all, gross hemolysis is unlikely in fingerstick samples.

Clotting. Clotting is a possibility. After you have taken the sample, the instruction is to test the cartridge and put it in the analyzer within 1 minute after you collected the sample. If the operator for some reason leaves the cartridge on the bench for a certain period of time, clotting could occur. If that cartridge is being put into the instrument, there are micro-clot detection features in the software that will detect this and abort the assay. It does happen. We have validated that the cartridge can actually stand on the bench for 5 minutes without causing any error of the sample.

What about operating conditions? Humidity and temperature. I illustrate this here with temperature alone, and temperature can affect both the analyzer and the cartridge. If the ambient temperature is outside of the operating temperature range for the analyzer, it renders itself inoperative and reports an appropriate message. That message could be if the instrument is too cold, it will say "heating." If the cartridge temperature is outside its limit, the test will be aborted. So incorrect operating conditions outside the specifications

will not affect the analytical results because test will be aborted.

What about test cartridge handling? What if the operator drops the cartridge? This could damage the cartridge, and if this happens, the analyzer camera will detect a damaged cartridge. However, it is more frequent that the sample will be lost in the capillary if you drop the cartridge. This is the part of the pre-checking before the cartridge is being processed. So if that happens, the assay and the test will be aborted. So in both cases, damage cartridge or loss of sample, the test will be aborted.

And in case the operator actually inserts a used cartridge once more and try to assay a sample, the analyzer camera will detect a used camera -- a used cartridge, sorry -- and the test will be aborted. So you cannot use a cartridge twice. It's impossible.

What could further go wrong when it comes to cartridge handling? There is a film on the top part of the cartridge where you are meant to handle the cartridge, as illustrated in the video. However, there are some optical windows on the cartridge, as well, and this needs to be according to specification because transmission measurements are performed in these windows. So in the situation where the operator contaminates a vital part of the cartridge with blood, with lotion, or with anything that could affect the transmission measurement, this will be detected in the pre-checking before the assay is started by the analyzer camera, and the test will be aborted if outside specifications.

What about operator skill level? Does it matter? You have seen the video, and the test procedure is extremely simple. The test is actually designed for CLIA-waived settings, so there is actually no need for thorough training in order to be able to run the assay. The only thing required is that you can read and follow the instructions. And the operator, again, cannot intervene when it comes to calibration nor for the cartridge -- neither for the cartridge nor the instrument itself. The analyzer also includes the option to set unique codes for given operators so that you actually can limit the access of the analyzer. And

after all, training materials, including instruction videos, are made available to customers.

And to further secure test quality, the labeling instructs the user to perform periodic external quality control testing, as regulated by local, state, or federal regulations. External control test results are stored in a separate log within the analyzer. And there is also a QC lockout function, which means that you can define your own QC scheme, and unless you follow that, you will not be allowed to run clinical samples.

So, to end this section, I would just highlight the fact that we, after 10 years on market with the CLIA-waived monitoring product, have had no MDRs. And also, referring to Dr. Scott, data from external QA programs indicate lab-quality performance in point-of-care settings outside of the lab.

I will in the rest of my presentation present Alere's proposed strategy to differentiate between the moderate-complexity test from the CLIA-waived test and also what prevents the former from being used in a CLIA-waived setting.

FDA has required Alere to clearly differentiate between the current monitoring test and the Dx test that we now seek clearance for. This table presents Alere's proposal to solve the challenge of differentiating between the two tests. On the right-hand side of the table, the monitoring product is being presented, and on the other column here, the new Dx test is shown.

The way to differentiate between these two is, first of all, to have different labeling on both of these two assays. They will also receive different ordering codes so you can separate the two through the ordering codes. And in addition to this, the use of the cartridges will also be regulated by the use of different configurations of the analyzer, one moderate-complexity analyzer and one CLIA-waived analyzer. And the effect of this is the fact that you can separate the two different tests through the catalogue number. You will also see that the new test, the Dx test, will only be possible to run on the moderately

complex analyzer. It can, of course, also run the monitoring product, but the opposite will not go because the CLIA-waived analyzer will only be able to run the monitoring product. The new Dx test will not be compatible with the installed base.

If we further look at some of the details of the two instruments, they will receive different catalogue numbers, and the configuration of the analyzers will secure that on the CLIA-waived analyzer, the only test that can be run will be the Alere Afinion A1c monitoring product, while on the moderately complex analyzer, all cleared Alere Afinion tests can be run, which means A1c and ACR at the moment.

So how can this prevent the new Dx test from being performed and used in a CLIA-waived setting? Yes, you have seen the video, and this is a short presentation of the current-waived assay and the test procedure. And it is simple. You just turn on the instrument, you open the foil pouch, take out the cartridge, and then the video started from the point where you took the sample, put the cartridge in, and you have the analytical result.

And what happens if you now start to use a Dx test in this setting? What happen is, first of all, that you have new labeling clearly stating that this is the Dx test. This shouldn't be used in this setting because this is a monitoring instrument. So it shouldn't be used here. However, if the operator continues to take the blood samples and put this cartridge inside the instrument, the instrument will actually record and abort the assay and inform the operator about the error, because the cartridge will not be processed in this instrument.

In the correct setting, where you use the Dx product with the moderately complex Afinion analyzer, what happens then is that you start the analyzer, you use the Dx product as well as the monitoring product. You take your sample. You put the cartridge inside the analyzer. But if you use the Dx cartridge, the analyzer will show you that you are using the

Dx. The progress bar here will illustrate that you are using the Dx assay. And after 3 minutes, the analytical result will be given out, but now with two decimal places, a test result with two decimal places.

Sorry. So could the Afinion A1c Dx be run in a CLIA-waived lab? No. As you have seen, it cannot, and there are distinct product ordering codes planned. The descriptions and CLIA statements in the labeling would prevent a CLIA-waived lab from ordering the moderately complex Afinion A1c Dx assay. And if an existing customer did somehow order the wrong test by mistake, the assay would not run on the current installed base with the current software version, and the product labeling would describe a different indication for use and CLIA statement alerting them to the error.

Thank you for your attention.

DR. SAN GEORGE: All right. Thank you, Frank.

And we're just about finished, folks. So let me just give you a quick summary of what we've presented here today.

You know, we showed you that there are tangible benefits with point-of-care testing for the diagnosis of diabetes. You know, we didn't talk so much how maybe especially that's the case in underprivileged and underserved communities. You know, Dr. Kahn did show you some low-hanging fruit, 1.4 million folks who were coming in to GP offices who might be assessed if there were a point-of-care system available. But as he also mentioned, there is 8 or 9 million Americans who are undiagnosed with diabetes, and the opportunity to reach some of them is what's presented with a point-of-care system. You know, we heard some concerns about maybe we wouldn't reach the most at-risk individuals in community screening settings, but I think we should consider the possibility that maybe we would, as well.

I think we've shown you that the Afinion A1c Dx test is accurate, precise; it exhibits

a total error less than 6%. I think we've shown that the likelihood of a false negative and a false positive is low, and that the risk to the patient in the event of a false negative or false positive are really minimal. I think we've shown that the sources of error have been effectively mitigated and that our approach to ensure that CLIA-waived laboratories could not use the moderate-complexity test, hopefully, we've demonstrated that to you satisfactorily.

In closing, you know, I would say that the Afinion A1c Dx clearance with moderate complexity, again, it requires sites perform QC, participate in PT, have laboratory-trained operators. It's really no different than the cleared central laboratory A1c tests.

CLIA waiver for the Afinion A1c Dx test would require that we demonstrate equal performance to the central laboratory in CLIA-waived settings with intended use operators. The FDA has very clear guidance on what needs to be demonstrated in order to gain CLIA waiver. There are flex studies that need to be conducted to demonstrate that the assay, and the system are robust to the kinds of areas that might occur in a CLIA-waived setting, operator errors and all kinds of other errors. We need to show that there's an insignificant risk of erroneous results. And there's clinical studies that are very clearly defined as to what needs to be -- how those need to be conducted and what kind of data need to be obtained in order to demonstrate also an insignificant risk of erroneous result. And we really only ask for the opportunity to generate those data and present them should they be presentable, assuming, of course, that the moderate-complexity clearance is granted.

You know, all point-of-care tests, A1c tests, they don't have the same performance. Some perform well. Some perform not as well. The same is true for laboratory systems. We wouldn't clear a system just because it's a laboratory system, and I think we would say a point-of-care system should not be not cleared just because it's a point-of-care system.

We as a manufacturer want to be judged on the merits of the performance of our system and not on the performance of other systems, and I think anybody would say that. So each system, whether it's point-of-care or central laboratory, should be judged on its own merits and not on those of its collective category.

And with that, I thank you for your attention and for your consideration. And we're happy to take questions at this time if there are any.

DR. WATSON: I thank the Sponsor and the Sponsor's representatives for those presentations.

So we will have an extensive Panel deliberation time after the FDA's presentation. But if anyone has any short clarifying questions right now for the Sponsor, we can take those.

Yeah?

DR. BURR: You all understand that I'm very grateful for indoor work on a day like this, but I've been sitting here listening to all this trying to figure out why we're here. What's the point of this? If a hospital lab wants to put an Afinion in their lab, they can do it and put any kind of QC umbrella around it they want. Nobody is going to take my two Afinion systems out of my office, which I depend on. And --

DR. WATSON: I think that might be better addressed to the FDA.

DR. BURR: Yeah. I mean, I don't care who answers the question, but I'd like somebody to.

DR. LIAS: Sure. So it's unusual for a professional society to include a statement about a type of test and say, you know, this test is not appropriate for a certain type of use. So this is the first time that the manufacturer has requested that we give a claim for the diagnosis of diabetes to a test intended for point-of-care use. And the ADA guidelines specifically recommend against point-of-care use. But it wasn't terribly clear to us what

the underlying concern was and whether that raised risks that should preclude us from -- that we needed to consider in determining whether or not the test was substantially equivalent.

And so we wanted to have some public discussions, one, to understand better what the concerns were behind the ADA recommendations against point-of-care use. And then second, as you'll hear in a little bit, the manufacturer has told us that they plan to seek CLIA waiver, and certainly, proficiency testing is one of the clear concerns. We wanted to hear some more discussion from the clinical community regarding the use of both moderate-complexity point-of-care A1c tests and whether there are risks we should consider when we get a regulatory submission for one of those, and then in the future, if we may get request for CLIA waiver, are there certain risks that we should think about in considering a CLIA waiver application?

I also want to clarify that we have not made a determination on whether the performance of this assay is substantially equivalent to other diagnostic assays. That decision hasn't been made. We don't have all of the data. That isn't part of our question about whether or not the performance of the test is substantially equivalent. However, if the Panel has thoughts in general about performance characteristics in general that you believe are important in answering these two questions, you can certain weigh in on that. But we are not asking the Panel to weigh in on whether this particular assay is substantially equivalent.

DR. BURR: Well, just a thought. I mean, you have to distinguish. There is point-of-care, which means that there might be a grown-up involved in the interpretation of the result, and then there's POS, or point-of-screening testing, where there are no grown-ups involved, and it causes more trouble than it's worth. And I think the ADA's concern is more about the POS testing.

DR. LIAS: Well, we wanted to find out some of that distinction. And also, we do think that there is some conflation of point-of-care and CLIA-waived, and they are overlapping but distinct.

DR. BURR: I understand that there are more -- there are moderately complex point-of-care testing --

DR. WATSON: I think if we can actually hold some of those questions till after the FDA presentation, that a lot of it will be clarified.

DR. KAHN: I wonder if I could just address for a moment, and I would encourage Dr. Ratner to do the same thing, with regard to this anomaly of the ADA saying one thing and the FDA saying another thing --

DR. WATSON: Actually, if we can hold that until the deliberations. Right now I just want some clarifying questions because we are going to --

DR. KAHN: Well, this will maybe clarify his point, and that is that at least in my tenure, the 25-year tenure, the ADA would always say what the -- it's a chicken and egg -- what the FDA said. In other words, if the FDA did not approve a medication or a device for a specific indication, the FDA [sic] said you should not use this. If the FDA said we approve a medication or device or a test for a specific application, the ADA always said we approve. So the ADA always -- there was never an exception. And maybe that's while I was there. Maybe it's changed. The ADA always followed the FDA in what they did.

When we started in 2006, the time I was there, and the ADA never had point-of-care testing for diagnosis, we said, well, point-of-care testing is not approved. And why was that? Well, because the FDA said there was no proficiency testing. We said, well, that's -- there's no proficiency testing.

DR. LIAS: Well, I would point out that that isn't true for hemoglobin A1c tests. The ADA recommendations for use of hemoglobin A1c for diagnosis preceded FDA's clearance

of tests for the diagnosis of diabetes. So, you know, I think in this case, the ADA was the initiator of this particular --

DR. WATSON: Yeah. And again, I don't want to get off on that. We'll have a long time to discuss this after the FDA's presentation. But any -- Dr. Rej?

DR. REJ: Some technical questions: Regarding storage of the cartridges, what are the recommended storage requirements?

DR. SAN GEORGE: So, very specifically, I'm going to ask someone else to give you those.

DR. REJ: Sure.

DR. SAN GEORGE: There's storage at refrigerated temperature that's allowed, and there's storage at room temperature that's allowed. And there's some combination that's allowed. And if you want the exact months for each temperature, I can get that for you. But it's certainly several months. It's over a year refrigerated, and it's a few months at room temperature.

Does somebody have?

DR. FRANTZEN: Yeah, 3 months at room temperature and 2 years refrigerated storage.

DR. REJ: Okay. And how does the device check on appropriate storage? You mentioned something about checking -- the camera checks the volume?

DR. FRANTZEN: Yeah.

DR. REJ: I'm not exactly sure how that checks the quality of --

DR. FRANTZEN: I mean, if the cartridge has been stored in an inappropriate storage conditions, for instance, too high a temperature so that some of the reagents have actually evaporated from the cartridge, that would be identified because that's one of the measures that the camera does before the assay is being started, which checking -- that's

one of the checks that you saw on the video listing checking. And one of those checks is to check volumes of the reagents. So if any of these volumes are outside specifications, the assay will be aborted.

MS. McCOLLISTER-SLIPP: So if something --

DR. REJ: So the stability is checked solely by the volume of the reagent?

DR. FRANTZEN: No. And then if something is going wrong with the chemistry, the pressure sensor, for instance, will also be used because if some of the reagents are affected and there are chemical changes in the reagents, those will affect the chemistry and some of the later steps in the procedure, which would be picked up by, for instance, the pressure sensors, and not only the sensor itself but also the pressure profile of the test. So there are a series of tests being performed and series of monitorations in order to check for inappropriate storage that could affect the chemistry of the assay.

DR. REJ: Okay. And it was also mentioned that there was a quality control component --

DR. FRANTZEN: Yeah.

DR. REJ: -- that is required? What is that? What is the manufacturer recommendation?

DR. FRANTZEN: Yeah, you can run -- there is two controls provided, and you can pick your own control scheme on the analyzer as you would like in the QC --

DR. REJ: So the frequency of testing is up to the operator -- up to the laboratory, or does the manufacturer have some recommendation?

DR. FRANTZEN: I have --

DR. SAN GEORGE: So I think the answer to that is, in the moderate-complexity setting, the CLIA regs specify twice a day or two levels each day, and the labs need to meet those regulations. And the wait setting, the manufacturer's recommendation is every 30

days, every new lot of reagent, and things of that sort.

DR. REJ: Right, but again, it should -- I believe that it states that it can be less rigorous than what the manufacturer recommends, so I'm just curious what your recommendation would be to your clients.

DR. SAN GEORGE: For which ones? The moderately --

DR. REJ: For moderate complexity.

DR. SAN GEORGE: I think they would -- we would tell them to follow the state, local regulations, whatever those are.

DR. REJ: Okay. Thank you.

DR. WATSON: Okay. Anna, did you have a question?

MS. McCOLLISTER-SLIPP: Oh, I was just sort of picking up on his questions about storage. I mean, one thing we've seen in the, like, for blood glucose meter testing is that, you know, a lot of vials or, you know, a whole bunch of vials of test strips will fall off a truck or whatever and then end up being used and being highly inaccurate, and there are really bad consequences.

DR. REJ: Right.

MS. McCOLLISTER-SLIPP: Now, people aren't going to be dosing insulin off of an A1c test, but I mean, so you're saying that the machine itself has QC mechanisms built in that would be able to test for any kind of extreme temperatures or the implications of some kind of extreme temperatures, or that sort of a setting?

DR. SAN GEORGE: Yeah, so there are such -- there are certain systems built in like that, as Frank was describing. You know, part of the flex studies that we would be required to do for CLIA waiver would be exactly of that type. We would have to stress the reagents way beyond the conditions under which they're supposed to be stored and show that under those conditions, an erroneous result is not given, that the analyzer would

recognize that and not give a result. So we'd have to generate those data.

DR. WATSON: Okay. Alan?

DR. REMALEY: Yes. Hi. Alan Remaley. Could you elaborate on the process by which you check your lots in terms of like calibration and how you tie back to NGSP? And also, do you check your end users in terms of once the lot goes out?

DR. FRANTZEN: Yeah, sorry. I think that the specialist on this area should actually do that elaboration, so if I could call for you, Cathinca?

MS. VARGMO: Hi, everyone. My name is Cathinca Vargmo. I'm also an employee of Alere Technologies and the global product manager for this assay.

So we have a collaboration, as Frank mentioned earlier, with the IFCC, a reference lab, the core lab of that network in the Netherlands. And we receive from them bimonthly a panel covering the measuring range, full panel, fresh samples that have been -- assigned with the three same secondary reference methods that you saw earlier in the publications that have also done. And we used those to monitor in-house reference. And we also used that to calibrate and monitor a range of the lots that we ship out into the market.

In addition to that, we also, as Frank mentioned, supervise various external quality control programs across the globe. You've seen results of some of those here, and we also participate ourselves in some of those programs, where feasible, as the operations side. It's based in Oslo, so it needs to be in a reasonable distance when we participate ourselves. So outside of those programs, results often are the same. We also participate in programs in the U.K., for instance.

And so we bring those results back into our QC and QA department to make sure that the quality of our products in the hands of the users and the results that they obtain in these programs are consistent with the data that we internally see when we release the lots.

DR. WATSON: Thank you.

Yes?

DR. NIPPER: I'm Dr. Nipper. And I have a question for the Sponsor about exactly how they envision these instruments being deployed in various GP offices. And I'm asking this not because I'm a clinical chemist, but because I'm a diabetic. I'm a type 2, and I've been a diabetic for about 15 years.

So I get my A1c monitored now by our central lab at Creighton, and I'm happy with that. But if I go to a new lab, say, I go to Dr. Burr who says he's got two --

DR. REJ: Good choice.

(Laughter.)

DR. NIPPER: -- who says he has two Alere instruments in his office, and one of them is a Dx -- which you perform the A1c to diagnose my diabetes, right? Would that be right, Dr. Burr?

(Off microphone comment.)

DR. NIPPER: Yeah. But then I go back to him for my routine monitoring. Would he use your waived instrument? So would he use the waived instrument, or would he use the Dx to monitor, to follow me?

MS. VARGMO: So what we are asking as intended use for our new product, the Dx product is to have both the --

DR. NIPPER: I'm asking --

MS. VARGMO: -- diagnostic and also the monitoring claim. So you would be able, then --

DR. NIPPER: Oh, okay.

MS. VARGMO: -- to use the Afinion A1c Dx both for diagnosis and for monitoring as a patient, so you could use that same cartridge and the same analyzer.

DR. NIPPER: I know you can use the same one for monitoring --

MS. VARGMO: Yes.

DR. NIPPER: But he was already on record for saying you're not taking his Aleres away from him so --

DR. WATSON: Okay.

DR. NIPPER: So would these instruments exist in the same office side-by-side? You wouldn't switch back and forth?

DR. SAN GEORGE: Not likely, not likely. So once somebody had the instrument for Dx, that would be the only one that they would have, and they would use it for diagnosis and for monitoring.

DR. NIPPER: Okay.

DR. SAN GEORGE: There would be no need for them to have two different ones.

DR. REJ: Just to fill in, we would not have a moderately complex instrument that --

DR. WATSON: Again, can we try to -- we're going to have a lot of discussion about this --

DR. NIPPER: Well, but I wanted to hear what the manufacturer had to say about how --

DR. WATSON: Yeah, exactly.

DR. NIPPER: -- they would deploy the instruments in a practice setting, whether you'd have the monitoring instrument, the waived instrument sitting on a bench side by side with the moderately complex instrument.

DR. SAN GEORGE: We don't see that happening, okay?

DR. NIPPER: Thank you.

DR. WATSON: Okay. Clarification?

DR. HENDERSON: I'd like to ask a question before you leave. For the operator,

what are each of those instruments -- what are they faced with for the price for each test? If an operator or GP or physician has these two tests or has these -- if they're going to consider having one or the other of these instruments in their office, how much would each test cost that operator to provide to their patients?

DR. REJ: I can tell you from my experience. Our net cost is a buck and a half per test.

DR. HENDERSON: But that's for the one you have. We're talking about the two -- now we're going to get one for diagnostic, and then we're going to have one, the screening. What's the cost differences?

DR. WATSON: Well, we aren't allowed to consider cost in a clearance decision, so I do want to clarify that.

All right. And we have one last clarifying question? No. We have two?

DR. WYNE: My question is actually kind of what he was asking, but I wanted to phrase it in a different way. So my understanding is that Alere as a company already has CLIA-waived assays already on the market in the United States, correct?

DR. SAN GEORGE: For monitoring.

DR. WYNE: So they're already selling this same device either for a moderately complex situation or a CLIA-waived situation?

DR. SAN GEORGE: For monitoring, that's correct.

DR. WYNE: Okay. So do you know of any circumstance where an office would purchase both machines and own both machines?

DR. SAN GEORGE: You know, I don't imagine that. So what I can imagine is -- and maybe one of our marketing folks should speak to this -- but what I can imagine is there's a moderately complex lab today who's running the Afinion for monitoring purposes. And when we get the -- if we should get the diagnostic claim, they would want to use it for

diagnosis as well. They would have to upgrade their analyzer either with the new software to allow them to run the Dx test, or we would have to swap out the analyzer -- excuse me. I don't imagine that they would have two analyzers, one for diagnosis and one for monitoring.

DR. WYNE: But the CLIA-waived one cannot be upgraded to allow the Dx test?

DR. SAN GEORGE: The CLIA-waived one cannot be upgraded to do the Dx test if the Dx test is only cleared for moderate-complexity use.

DR. WYNE: Okay. And this is relevant to the point where you said there's also the catalogue numbers. So, in theory, if someone owns the CLIA-waived device, they would not be allowed to place an order for those cartridges, in theory?

DR. SAN GEORGE: Correct.

DR. WYNE: Okay. So my other question is you showed us all this data from Sweden and Switzerland and so on. What I wasn't fully clear on is the data you're showing us from those countries, are they doing the testing in what would be equivalent to us being CLIA waived, or was that data from labs that were the equivalent of moderate complexity, not CLIA waived?

DR. SAN GEORGE: Dr. Scott?

DR. SCOTT: In Switzerland, the PT testing is required. In Norway, it's voluntary. And in Sweden, remind me?

MS. VARGMO: Also voluntary.

DR. SCOTT: Also voluntary. And these are GP offices. So in Norway, Sweden, it would be very comparable to a waived setting because -- and the --

DR. WYNE: Probably but --

DR. SCOTT: -- PT is not required. But obviously in those two countries, participation is quite high. It's not required. In Switzerland, it is required.

DR. WYNE: So really what you're saying is you think, essentially, those are not equivalent to a CLIA-waived because they participated --

DR. SCOTT: Well, I think I tried to make that point when I diverted from maybe Sweden, Switzerland, Norway is not exactly the same as GP offices in the U.S. running under a waived setting. And the whole waived thing is really we were asked to think about it, but this particular submission is for a moderately complex environment.

DR. WYNE: I understand. Thank you.

DR. WATSON: Okay. And did you have a question?

MS. McCOLLISTER-SLIPP: Yeah. I mean, just thinking about the potential people from -- you know, you're using all this data from Sweden and Norway. Those are pretty ethnically homogenous societies. I mean, given some of the concerns are about ethnic differences, do you have any kind of numbers about the diversity of the people upon which your validity tests are made?

DR. SCOTT: Totally irrelevant with regards to proficiency testing. They are getting samples with assigned values. Now, the race and ethnic issues actually reflect where the cut points should be for that particular race or ethnic group. It has nothing to do with performance of the test. It's where the cut point should be.

DR. WATSON: Okay. Thank you.

One last clarifying question?

DR. McSHANE: But going back to her point, so we saw numbers like 70% of the labs tested in the exercises passed. So you're telling us that many of those labs, in fact, underwent proficiency testing so that they -- or the equivalent of it, so that it's sort of an indication that even moving to the moderately complex situation doesn't solve those problems. Now, your new machine might solve those problems --

DR. SCOTT: Maybe I'm -- let me just ask Rick if I can say this. So the two

instruments are the same. They only differ by software. The two cartridges are the same. They only differ by labeling.

DR. McSHANE: Right.

DR. WATSON: They only differ by what?

DR. McSHANE: But doesn't the software have additional checks in it?

DR. SCOTT: I'm sorry?

DR. McSHANE: Does not the software have additional checks in it?

DR. SCOTT: The only check is to make sure that a monitoring cartridge is not inserted into it.

DR. WATSON: So what I understood is that one cartridge won't even fit.

DR. SCOTT: It'll fit, but it won't be read because of the barcode.

DR. McSHANE: So the results we saw with the 70% pass rate in different countries, granted, where we think a large portion of those labs, or even GP offices, would have undergone some kind of equivalent of proficiency testing?

DR. SCOTT: Well, the 70% group that you're referring to is the Norwegian study, which is Sverre Sandberg's proficiency testing program.

DR. McSHANE: Right.

DR. SCOTT: Participation is voluntary.

DR. McSHANE: Um-hum.

DR. SCOTT: But the *n* for the Afinion users, of the 1,280-something GP offices, the *n* for the Afinion was around 600. So 600 offices using the Afinion in Norway -- I'm trying to make sure I get this right -- the minimal training required for an operator is 3 years of high school, which is at least defined, whereas in the U.S. and Switzerland, there are no educational requirements. So it's pretty comparable to a waived setting, but they are voluntarily participating.

DR. WATSON: Okay. All right. And I will remind you, we will have additional time to ask questions of the Sponsor.

But I'd like us to take a break now. We're 5 minutes late. So if we could all come back at -- what time -- 10:50, we'll resume with the FDA presentations, and then, again, after all of the presentations, we can still ask questions of everyone. Thank you, guys.

(Off the record at 10:37 a.m.)

(On the record at 10:55 a.m.)

DR. WATSON: I think we have all of the Panel members present, so I'd like to call the meeting back to order. The Panel members will see that they have a little show and tell at their desk. We've got a cartridge just to look at to see what we've been discussing.

But now I think we're ready for the FDA presentation. So please go ahead.

DR. LESSARD: Good morning. My name is Juliane Lessard, and I am the FDA lead reviewer for the 510(k) submitted by Alere for their Afinion HbA1c Dx test system.

As you heard, Alere currently offers a hemoglobin A1c point-of-care assay called the Afinion HbA1c. This test was cleared by FDA in 2005 for measuring the percent HbA1c in capillary fingerstick and venous whole blood to track long-term glycemic control in patients with diabetes. Earlier this year, the Sponsor submitted a 510(k) to add a new diabetes diagnostic claim to this existing Afinion HbA1c assay. This 510(k) is the subject of today's panel meeting.

And for today's presentation, I will first discuss some of the regulatory history surrounding HbA1c tests. Then I will address the different settings in which HbA1c testing is performed today, with a special emphasis on CLIA complexity and proficiency testing requirements. After that, I'd like to introduce the concept of point-of-care testing and briefly discuss some perceived advantages and disadvantages of point-of-care testing environments. This first part sets the stage for the first panel question. Then I will

reiterate some of the commonalities and differences between the existing monitoring Afinion HbA1c assay and the proposed diagnostic version, which directly relates to Panel Question 2. And finally I will briefly touch on the concept of CLIA waiver by application, which relates to Panel Question 3.

The new diagnostic assay described in the current 510(k) is called the Afinion HbA1c Dx, and just as a reminder, Alere is seeking a new claim to use this test as an aid in the diagnosis of diabetes as well as to identify patients at risk for developing diabetes. The Afinion HbA1c Dx is a point-of-care assay to be used in moderately complex laboratory settings.

From a regulatory perspective, there is a big difference between HbA1c assays intended to monitor long-term glycemic control in people who already have diabetes and HbA1c assays intended to diagnose diabetes and pre-diabetes. Since the Medical Device Amendments of 1976, HbA1c assays were traditionally used and cleared by FDA for the long-term monitoring of HbA1c levels in patients with diabetes to see how well they were managing their condition.

In 2010 the American Diabetes Association began to recommend that HbA1c testing can be used to diagnose diabetes and pre-diabetes in patients without a prior history of diabetes. Accurate results near the clinical decision points are necessary for safe use of these tests for diagnosis.

Since not all monitoring assays are accurate and precise enough to be used for the diagnosis of diabetes, FDA created a separate regulation for HbA1c assays specifically intended for the diagnosis of diabetes as a way of identifying those tests that demonstrated adequate performance for diagnostic use. The first diagnostic HbA1c test was cleared by FDA in 2013. Since then, a total of eight assays have been cleared as an aid in the diagnosis of diabetes and to identify patients who may be at risk for developing

diabetes in the future. In comparison, there are approximately 38 monitoring HbA1c assays currently marketed in the U.S.

There are a number of specific performance requirements that diagnostic HbA1c assays need to meet before FDA can clear such a device for marketing. Sponsors must demonstrate that their device has equivalent performance to a legally marketed diagnostic HbA1c predicate device with a focus on the following requirements:

Devices must be precise, devices must be accurate, and the total error of test results when compared to a standardized method cannot exceed 6%. Devices must also have little to no chance of giving false test results for samples that contain common hemoglobin variants. And finally, diagnostic HbA1c devices must maintain an initial and annual certification with a glycohemoglobin standardization organization, for example, the NGSP.

At this time, all diagnostic HbA1c devices have been cleared for use in central laboratory settings.

As you heard earlier this morning, current clinical guidelines from the American Diabetes Association recommend against using point-of-care HbA1c assays for the diagnosis of diabetes.

The Afinion HbA1c Dx test system is intended for the diagnosis of diabetes in moderately complex point-of-care settings. At today's panel meeting, FDA is seeking input from the clinical community on two distinct issues. First, are there new risks introduced when HbA1c tests are used in point-of-care settings that should be mitigated prior to FDA clearance? And second, what issues should be addressed in diagnostic HbA1c tests that are intended for use in CLIA-waived point-of-care settings?

In the previous presentation, the Sponsor highlighted some of the performance characteristics of the Afinion HbA1c Dx test. However, please be aware that FDA has not

yet received all the data needed to complete the evaluation of the Afinion HbA1c Dx test system performance. The performance characteristics of this test are unknown. Today's discussion should only focus on the setting in which this test may be used rather than what its performance is. Therefore, for the purpose of this Panel meeting, please assume that the performance of the Afinion HbA1c Dx system is comparable to the performance of other diagnostic HbA1c tests currently on the market.

I would like to emphasize again that just like for any 510(k), FDA will not clear the Afinion HbA1c Dx assay for marketing unless the Sponsor can demonstrate that its performance is substantially equivalent to other cleared diagnostic HbA1c devices.

HbA1c tests for monitoring patients with diabetes are conducted in a wide variety of different environments, including central laboratories, the emergency room, physicians' office laboratories, and community clinics. These environments have very different levels of resources and expertise. To distinguish, regulate, and standardize them effectively, the Clinical Laboratory Amendments, or CLIA, were created in 1988. Adherence to the CLIA standards is enforced by the Centers of Medicare and Medicaid Services.

One of CLIA's main objectives is to establish quality standards for laboratory testing, which means that every test result reported to a patient should be reliable, accurate, and timely. Any laboratory that performs testing on human specimens, for example, blood, urine, or tissue, for the purpose of diagnosis, prevention, or treatment of disease, or assessment of health, must be certified under the CLIA regulations. Every in vitro diagnostic test falls into one of three CLIA categories: waived, moderate complexity, or high complexity. The type of CLIA certificate that a lab obtains determines the complexity of tests it is allowed to run.

Based on the level of resources and expertise, CLIA distinguishes three different types of clinical laboratory testing sites. Sites covered by CLIA Certificates of Waiver are

subject to only minimal regulations. At these sites, anyone can perform a test according to the manufacturer's instructions for use. There are no proficiency testing requirements to verify the accuracy of test results, no quality control requirements beyond those listed in the test package insert, and the Centers of Medicare and Medicaid Services inspect only about 2% of the thousands of waived testing sites each year. Out of the more than 250,000 laboratories currently covered by CLIA, almost 70% are waived testing sites.

Laboratories performing moderate or high-complexity tests must comply with specific laboratory standards governing certification, personnel training, proficiency testing, patient test management, quality assurance, and quality control. These sites are also subject to regular inspections by CMS.

The type of tests laboratories may perform depends on their CLIA certificate. Sites with a CLIA Certificate of Waiver may only perform waived tests. Waived tests are simple tests with a low likelihood of erroneous test results. In vitro diagnostic tests may be CLIA-waived because they are an over-the-counter product, such as urine pregnancy tests, or a manufacturer may apply for a CLIA waiver for their device.

Moderate-complexity lab tests typically involve several reaction steps, such as separating blood into serum or plasma, are often run on large, automated clinical chemistry analyzers, and require a moderate level of expertise from lab personnel.

High-complexity tests are complex tests requiring a high level of operator expertise and training, for example, DNA sequencing. In addition, any test that has not been CLIA-categorized or a cleared test which has been modified by the laboratory is by default considered a high-complexity test.

The American Diabetes Association specifically highlighted proficiency testing in their talk and guidelines. Proficiency testing, in general, determines and compares the performance, for example, accuracy and precision, of individual laboratories on unknown

test samples provided by a proficiency testing program. Proficiency testing is designed to ensure ongoing quality of test results and evaluates test performance in a realistic clinical environment. In the case of HbA1c, proficiency testing should be performed at least two times per year to verify test accuracy, and it is only required in moderate and high-complexity labs, not in CLIA-waived settings.

I'd also like to point out that proficiency testing results for hemoglobin A1c typically only reflect the use of venous blood samples, not capillary fingerstick blood samples.

One example of hemoglobin A1c proficiency testing programs in the U.S. is the CAP survey, which is the proficiency testing program recommended by the American Diabetes Association. Twice or three times a year, the CAP survey mails out three to five pooled, fresh venous whole blood samples to participating laboratories. The samples span a wide range of HbA1c values, and their target values are assigned by the mean values obtained from all standardized reference labs in the NGSP network. The laboratories analyze the proficiency testing samples as if they were real patient samples and report the results back to the CAP survey. To pass, at least two out of three samples must have an accuracy within 6% of the sample target value. For each participating HbA1c test method, the CAP survey publicly reports accuracy and between lab precision.

Point-of-care testing typically refers to the use of an in vitro diagnostic test outside of a traditional central laboratory and near the site of patient care. Common point-of-care testing sites include physician office laboratories, emergency departments, intensive care units, operating rooms, and community health screenings, including diabetes clinics.

These point-of-care settings include varying levels of clinical laboratories. In CLIA-waived point-of-care settings, such as community health screenings, tests may be performed by anyone. In other point-of-care settings, such as physician offices, nurses or nursing assistants may perform the tests. Physician office laboratories are typically either

moderate-complexity or CLIA-waived environments. In moderate-complexity point-of-care settings, such as the emergency room of a large hospital, tests are performed under the oversight of a qualified laboratory medical director with requirements for personnel training and proficiency testing.

In the case of HbA1c, advocates for POC testing, as well as the current clinical guidelines from the American Diabetes Association, emphasize the advantage of having access to accurate and precise tests while patients are interacting with their healthcare providers. Several studies have shown that point-of-care HbA1c testing improves patient engagement and can lead to more timely treatment decisions and ultimately overall better glycemic control.

In contrast, those who oppose point-of-care testing generally raise concerns about the accuracy and reliability of the testing, especially in CLIA-waived point-of-care settings where testing may be performed by anyone. Primary literature suggests that the success of point-of-care testing may often be directly related to the level of user training. The more expertise laboratories have, the more likely they are to produce consistent results. More skilled users may also be more likely to recognize inaccurate test results, to identify possible causes for such results, and to mitigate them appropriately.

As mentioned earlier, the ADA currently recommends against the use of point-of-care HbA1c tests for the diagnosis of diabetes. Based on the information presented so far by the ADA, Alere, and FDA, we would like to pose the following questions to the Panel:

Does the Panel have any concerns about risks to health regarding the use of point-of-care HbA1c devices in general, irrespective of CLIA complexity, for the diagnosis of diabetes? If so, please describe these concerns.

Does the Afinion HbA1c Dx test system, with an intended use in moderate-complexity point-of-care settings, raise any new concerns about risks to health? If so,

please describe these concerns.

And if the Panel has concerns about risks to health for a or b above, what mitigations, if any, may be implemented to address those concerns?

Let's switch gears a little and consider the test system itself.

As Alere discussed in their presentation, they currently market the Afinion HbA1c test system. This test is CLIA waived and has been in clinical point-of-care use in the U.S. for about 10 years. The Afinion HbA1c test available today is cleared for the long-term monitoring of glycemic control in patients with diabetes. It is not yet cleared for diagnostic use, and I'd like to re-emphasize that FDA has not yet completed the performance review of the proposed diagnostic version.

The proposed diagnostic version of this test, the Afinion HbA1c Dx, is in many ways identical to the monitoring version on the market today. The sample types and collection method is the same, the diagnostic test uses the same reagent formulation as the monitoring version, and the AS100 analyzer is the same instrument for both tests with regards to name, sample processing, results calculation algorithm, quality control lockout control, and user manual.

However, as Alere described in their presentation already, there are a few differences between the current CLIA-waived monitoring Afinion HbA1c test and the proposed diagnostic Afinion HbA1c Dx assay. The letters "Dx" have been added to the name of the diagnostic test system, and it is available under a different catalog number and description. The diagnostic reagent cartridge also contains a different unique barcode and is accompanied by a package insert specific to the diagnostic test.

The Sponsor proposes to create two versions of the analyzer to avoid accidental use of the Afinion HbA1c Dx assay in CLIA-waived point-of-care environments. The two versions have the following differences:

At startup, the CLIA-waived analyzer displays "CLIA waived." The CLIA-waived version only accepts reagent cartridges with a barcode specific to the monitoring assay. The diagnostic cartridge cannot be run on the CLIA-waived version. In contrast, the moderate-complexity analyzer version can run all cleared Afinion tests, including the monitoring Afinion HbA1c and the diagnostic Afinion HbA1c Dx assays. And although both analyzers are accompanied by the same user manual, there is a different quick guide for each, which states the appropriate test complexity. And finally, the CLIA-waived analyzer displays results with one decimal point, whereas the moderate complexity analyzer displays results with two decimal points.

The Sponsor has proposed a number of ways to separate their current CLIA-waived monitoring HbA1c test from their proposed moderately complex diagnostic HbA1c test. However, laboratories in the clinical community will be aware that the Afinion HbA1c diagnostic test and the current Afinion HbA1c monitoring tests are the same test with two different names.

Therefore, we pose the following question to the Panel members:

Is the Sponsor's proposed strategy to differentiate the current CLIA-waived monitoring Afinion HbA1c test system from the proposed Afinion HbA1c diagnostic test system adequate to address concerns about the use of point-of-care monitoring HbA1c tests to diagnose diabetes in CLIA-waived settings by untrained personnel?

The currently marketed monitoring Afinion HbA1c test was CLIA waived by application in 2006 and is primarily used in CLIA-waived point-of-care sites. The sample matrix most commonly used in these CLIA-waived point-of-care settings is capillary blood from a fingerstick.

The Afinion HbA1c Dx, as described in this 510(k), is intended for use in moderate complexity laboratories. However, the Sponsor has indicated to FDA that they might apply

for a CLIA waiver for the Afinion HbA1c Dx in the future so that it can be used in any testing environment.

To obtain a CLIA waiver, sponsors need to demonstrate that their device is simple and carries an insignificant risk of an erroneous result. Sponsors should assess all potential sources of error that could lead to a false test result. This can include user errors, device malfunctions, for example, due to insufficient sample volume, and environmental influences, such as temperature and humidity. To mitigate each error source identified, sponsors should integrate appropriate design elements, such as failsafe mechanisms, alerts, and warnings into their device. In order to obtain a CLIA waiver, sponsors need to demonstrate to FDA that these mitigations work as intended to successfully prevent the reporting of false test results.

Sponsors also need to provide the results of a clinical study comparing their device to a standardized reference method. This study should include more than 360 samples, of which two-thirds must be unaltered, fresh patient samples. At least nine untrained users representative of a CLIA-waived environment should perform the study over a period of 2 weeks or longer. Per FDA's CLIA waiver guidance, to be granted CLIA waiver, at least 95% of test results should fall within a clinically acceptable error range, and none of the results should have errors large enough to pose a risk to patient safety.

Since there is a possibility that FDA will receive a CLIA waiver application for the Afinion HbA1c Dx test in the future, please consider the design of this test system to address the following questions:

Please discuss the potential advantages and disadvantages of using this test as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes in CLIA-waived point-of-care settings.

If there are any risks to health associated with the use of this device in CLIA-waived

point-of-care settings, are there potential mitigations that may be employed by the manufacturer that are adequate to address these risks to health?

And with that, I'd like to thank you for your attention, and I'll be happy to take questions.

DR. WATSON: Thank you very much.

So we have some questioning for the FDA, clarifying questions, before we begin our deliberations? Any?

DR. NIPPER: I have a question. I was reviewing the -- I'm Henry Nipper. I was reviewing the ADA guidelines as provided to us in the packet, and I'm concerned that the quote there is not in context because, as I read it, it says, "Although point-of-care A1c assays may be NGSP-certified, proficiency testing is not mandated for performing the test, so use of point-of-care assays for diagnostic purposes is not recommended."

I think that that -- I wonder if once you put in the proficiency testing requirement as moderate complexity, whether you see that recommendation as not being particularly applicable to the situation?

DR. LESSARD: So I will say that the reason the quote is cut short was for clarifying purpose -- for clarity purposes on the slide.

DR. NIPPER: Yes, yes.

DR. LESSARD: And also part of the reason we're here today is because we are not -- we were not clear what are all the reasons that the ADA is recommending against use of diagnostic HbA1c assays in point-of-care environments.

DR. WATSON: I'd like to actually bring in Dr. Ratner at this point. You had a very nice presentation this morning. Is there further clarification you can give to Dr. Nipper's question?

DR. RATNER: So in my presentation, the entire quote was there.

DR. NIPPER: Yes.

DR. RATNER: And the emphasis on the proficiency testing is absolutely inherent in the recommendation.

DR. NIPPER: I read right from the recommendation, so I agree.

DR. RATNER: So we do view the proficiency testing as being a critical aspect of the utilization of A1c for diagnosis.

I think it's also important to recognize the difference between monitoring and diagnosis here. What I've tried to do in my presentation was to discriminate monitoring and diagnosis and the categorical nature of diagnosis as opposed to the continuous nature of monitoring, and then to separate out the point-of-care aspects from a central lab component.

I think that Dr. Burr made a very important distinction between point-of-care and point-of-service and the ability to oversee what's going on. Many physicians' offices, my old one included, actually functioned under moderate-complexity rules. And we had our point-of-care A1c that met those characteristics. There is a very great concern about community-based utilization of point-of-care machinery in which the oversight and the quality metrics are not met, and yet they have a huge impact within the community. So that is the other aspect of really emphasizing the proficiency testing and the oversight of quality control.

MS. McCOLLISTER-SLIPP: But if I understand it, and I'm a little under-caffeinated and exhausted and my blood sugar is high, so I might be a little bit dense today, but if I understand it, it sounds as if this application includes all of the proficiency testing as part of the application, correct, for the diagnosis?

DR. RATNER: So I want to emphasize that I was neither asked nor did I review the application --

MS. McCOLLISTER-SLIPP: No, I know, I know, I know. It was more for FDA than you --

DR. RATNER: Yeah.

MS. McCOLLISTER-SLIPP: But yeah. I mean --

DR. LESSARD: Yes. The 510(k) application is for use in moderately complex laboratory settings, which would include proficiency testing.

DR. WATSON: But the third question that the FDA asks us to address is future considerations, so should they apply for CLIA waiver in the future; is that correct?

DR. LESSARD: Yes, that's right.

DR. HENDERSON: To apply for CLIA waiver, they wouldn't take away the proficiency testing? I mean --

DR. WATSON: CLIA waiver would take away proficiency testing.

DR. HENDERSON: Oh.

DR. WYNE: I have a question, actually, again, for Dr. Ratner. So I understand about your concern, but do we have any data on the impact of the accuracy of the testing if it's done in the type of setting that the ADA is concerned about? I mean, is this an expert opinion, or is it a data-driven consideration?

DR. RATNER: So there are very good data on the value or lack thereof of community-based screening for diabetes. There, we have very solid data, and the recommendation of the American Diabetes Association is to do opportunistic screening within the setting of healthcare delivery, not community-based screening.

Again, the concern here is the utilization of technology outside of the setting in which it was intended.

DR. WYNE: So we don't have data that it will not be accurate in the setting outside of which it was intended?

DR. RATNER: For community-based screening, no, we have no data.

DR. WYNE: Okay.

DR. RATNER: I think that when -- the FDA is probably the better authority to address this, the question of at what point is a test really able to move from a moderate complexity down to a waived test. And that's really the question that you're asking.

DR. WYNE: Yeah, because I think what you're saying is something fundamental I learned in school, which is for testing, you want a very simple, inexpensive, accurate test of a highly prevalent condition, and glucose testing in a screening setting meets that epidemiological kind of criteria. It's inexpensive. It's easy to do. It's very accurate, right?

DR. RATNER: Correct.

DR. WYNE: And so we've got a test that does that in a community setting that's much cheaper.

DR. KAHN: To address that point, if I may, I think the ADA for many, many years has been against all tests and devices used in a community health fair setting. They use precious resources of healthcare. They're often done by untrained operators. A glucose meter has been repeatedly used -- in fact, that's the most common device used at a community setting to measure someone's blood glucose. ADA has been against using the meter in a community healthcare setting. That's different from a healthcare provider. It's community screening. They've always been against community screening. So I think the glucose test is no different than the A1c test. And certainly, in my long tenure, and I think now both tests, all tests, lipid tests should not be used at community health fairs. And that's the issue.

DR. WATSON: Dr. McShane?

DR. McSHANE: Yeah. So I just want to follow up a bit on Kathleen's question. And I started asking this question earlier, but I want to come back to it. So there have been

tests, for example, the ones conducted in Norway, Sweden, Switzerland, where they have been put through a proficiency test, and roughly 30% of the labs did not pass. So the question in my mind is of those 30% that did not pass, were they the ones who did not operate in the context of what we would consider a moderate-complexity environment with proficiency testing, or is there no association? Anyone?

DR. SCOTT: There's no breakout of the ones that did not pass, but I'll remind you that 30% of the central laboratories in that survey also did not pass.

DR. McSHANE: And that actually gets to my point. So it seems like we're equating poor performance with whether you operate in this moderately complex environment, but I'm not sure we have the data to suggest there is a correlation there.

DR. SCOTT: I would agree.

DR. McSHANE: And maybe that a particular test, you know, perhaps this company's test -- I don't know -- you know, is so good that it's basically idiot-proof.

DR. SCOTT: Well, I --

DR. McSHANE: And then it wouldn't --

DR. SCOTT: -- debated whether to use that word in my talk or not and decided not to.

(Laughter.)

DR. McSHANE: But that's what I'm struggling with, if you've got no data to really assess that question.

DR. WATSON: Okay.

DR. SCOTT: Real quick, the use of glucose meters in community screening -- and Courtney, remind me if I'm wrong -- but there's not a single glucose meter that's cleared for diagnosis. All the community screening using glucose meters is off-label.

DR. WATSON: Any further questions?

DR. BURR: Can I add something? The whole basis of this discussion is based on an absurdity, which is that there's some magic about an A1c of 6.5%. There's no material difference between someone with an A1c of 6.4, 6.5, 6.6, 6.3. So the idea that there's this arbitrary cut point and that all of this energy is being expended for a test to be diagnosis is a little silly and misses the point. The ADA is part of the problem. Not the first time that's been true. And more helpful information would be provided by a paradigm algorithm approach to deciding when someone has clinically significant hyperglycemia or not based on all kinds of information, not just the A1c. So the whole premise here is very fragile and is leading to some trapping people in corners that are unnecessary and a little absurd.

MS. McCOLLISTER-SLIPP: But again, coming from the perspective of a patient -- I mean, that's my role in this Advisory Committee -- I think Dr. Ratner's points -- I mean, there's a question at hand, and then there's what happens in the real world based on the decisions the FDA makes. And there are some real concerns about things like life insurance, you know? Hopefully, we will keep the Affordable Care Act after this election cycle and people will still be able to get access to healthcare regardless of preexisting conditions, but there are real-world implications. And once these things kind of get decided, they get calcified. So FDA isn't involved in any of those discussions, and that's appropriate, but what we decide here or what they decide with what we tell them has real-world implications. Now, whether or not you want to create a scale or an algorithm, I think that's a different discussion, but we can't pretend that what we're talking about doesn't actually impact people very directly.

DR. WATSON: Dr. Ratner?

DR. RATNER: So, Dr. Burr, I completely agree with what you've said. We've made categorical cutoffs on a continuous variable.

DR. BURR: Right.

DR. RATNER: And it's essentially based upon the data shown here. It came out of three different population studies, the NHANES, the Egyptian study, and the Nauruan study. And the relationship between hyperglycemia and the prediction of very, very specific diabetes-related retinopathy has a step function to it. Where you establish that step is consensus. So if you look at the slide shown here, you could actually say an A1c of 6.2 is the point at which your risk of retinopathy goes up, and that correlates with a fasting of 120, not 126 --

DR. BURR: Right. I mean, but, you know, grown-ups, I mean, who understand this intervene long before 6½ shows up in the idea they're going to prevent 6½ from showing up. It gets very, very confounded. And hanging something on that arbitrary number in an environment where A1c is affected by intervention long before people achieve a 6.5 makes -- it creates complications like this session here today.

DR. RATNER: It does. However, I would suggest that there are a lot of reasons for categorical definitions as opposed to rolling levels, both in terms of indications from the Agency for intervention as well as providing educational guidelines for practitioners. Arbitrary though they may be, with large error bars around them, once we make a diagnosis of diabetes, it has significant implications for the individual, for their family, for their employer, and for society. And I think that really becomes a major issue from a diagnostic standpoint as opposed to a management standpoint.

DR. WATSON: Dr. Wyne?

DR. WYNE: You know, I agree with the idea that the number -- you had to pick a number at some point, but an interesting piece of what struck me as you're talking about it is does it make a difference if the A1c is 6.4 or 6.51? What Dr. Kahn told us is the only difference is that they might get prescribed a statin that day, but management is not any different. And actually, if you look at our guidelines, we've always struggled with the

question of, well, we're diagnosing at 6.5, but we're told that the target is below 7. So that means we actually don't initiate any pharmacologic therapy at diagnosis when it's such a close diagnosis.

So does it really matter if you're using a machine that has this huge false negative coming up at 6.38 or 6.48? And I don't know the answer, but I think it's something that we're struggling with.

DR. RATNER: The therapeutic guidance of aiming at 7 was based upon the DCCT showing a reduction in complications as you approach 7. Remember, they never got there, and the goal was considerably lower.

The limitations in terms of the goal of therapy is based upon the risk of hypoglycemia. That's clearly a moving target. If, in fact, we could safely achieve glucose levels solidly within the normal range, I don't think there's a practitioner around who would argue against it if we could do it safely.

DR. WYNE: But Dr. Kahn just told us it doesn't matter. Over 20 years, it doesn't have to be below 7.5, but that was using Swedish and Australian data, and that is not American patients.

DR. WATSON: Can I get in here now? Before we continue with complete discussion, I'd like to just ask for clarifying questions now because we do have some public comments that I'd like to incorporate into our complete discussion. So if there are any further clarifying questions for the FDA, can we have those?

MS. McCOLLISTER-SLIPP: So the point of what we're trying to decide today is based on the data they've given us; is this equivalent to the laboratory test, correct? I mean, based on, you know -- is the diagnostic machine that they want to market as a diagnostic machine, is it consistent with the kinds of tests that you would get from a laboratory-based test?

DR. WATSON: Well, there are three questions -- and we can go over those again before we start -- while we're doing deliberations, and that's not exactly what the questions were.

Okay. All right. I'm sorry for limiting. I want to keep us on time, and also, I want us to hear all of the information, including public comment before we start our full discussions.

So are there any other clarifying questions?

MR. THURAMALLA: Naveen Thuramalla. So I have a small confusion, and I think -- maybe even the Sponsor. So if a lab today has the monitoring device that they've been using regularly, that's a CLIA-waived device. But if tomorrow they decide to buy the new device whenever that gets cleared, that would be for monitoring and diagnosis. That would not -- that would require proficiency testing?

UNIDENTIFIED SPEAKER: Right.

MR. THURAMALLA: So what would happen to that facility if they only have the Dx version, which can also do monitoring? The person who was doing the testing all these days may not have been qualified at a proficiency testing level. So will he or she be disqualified from continuing doing the testing, or how would they differentiate that the test is being done only for diagnosis and not for monitoring? So I'm a little bit confused how that differentiation would be made.

DR. WATSON: I think that's one of the FDA's questions, because we know it's the same machine that can give the same kind of information. The difference is in the cartridge, but the cartridge is what the clinician buys. So if they buy the right --

DR. LIAS: That may be something you all want to discuss, what you just asked, later. Our question is actually more about if a waived lab just hears about this type of clearance --

DR. WATSON: Right, which is --

DR. LIAS: -- will they just do it off-label? And is that part of the concern? Mainly, the questions are really quite simple.

DR. WATSON: Yeah.

DR. LIAS: I wouldn't over-think them, you know?

DR. WATSON: I agree. So I agree with you.

DR. LIAS: Surrounding the term "point-of-care."

DR. WATSON: Because everyone will know that this is the same machine giving the same information. It's just whether or not you get the cartridge which will allow you to say Dx or not. And the question is do we have enough controls in place to make sure we're satisfied that that's safe to do.

Is that a fair assessment?

DR. LIAS: Does the fact that it's a point-of-care introduce any new risks that we should consider in determining substantial equivalence?

DR. WATSON: Okay. And if we're through with the clarifying questions, I'd like to ask if -- we have one person registered for public comment, and since we're running a little ahead of time, is that person present? Would you be ready to give -- deliver -- okay, if you would please come up?

Okay. Please introduce yourself, and actually, I have to have Lieutenant Commander Garcia read something to you first.

LCDR GARCIA: Thank you, Dr. Watson.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA

encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Watson?

DR. WATSON: Thank you very much.

Please introduce yourself.

MS. CALLEJA: Good morning. Thank you. My name is Khatereh Calleja. I have no financial interests or stake in this specific test or this specific product.

My name is Khatereh Calleja. I'm Senior Vice President of Technology and Regulatory Affairs at AdvaMed. And I'm here today representing AdvaMed Diagnostics, or AdvaMedDx.

AdvaMedDx member companies produce advanced in vitro diagnostic tests that facilitate evidence-based medicine, improve the quality of patient care, enable early detection of disease, and reduce overall healthcare costs. Functioning as an association within AdvaMed, AdvaMed is the only organization that deals exclusively with issues facing in vitro diagnostic companies both in the U.S. and globally.

We appreciate FDA's holding of this Panel meeting. We support this important discussion on hemoglobin A1c, or HbA1c, testing and diagnosis of diabetes and point-of-care intervention.

Point-of-care technologies play a critical role in helping diagnose life-threatening and chronic disease in the U.S. and globally. We commend FDA's efforts today to hear from the scientific community and consider these issues to help support access to the latest technologies for patients. Vital tests, such as HbA1c, improve patient care and provide timely and useful clinical information to support early detection and accurate diagnosis.

Such tests are revolutionizing healthcare by enabling laboratory testing at the hospital bedside, health center, clinic, physician's office, and other clinical settings. They can result in better patient care through accelerating clinical decision making and enabling more timely treatment decisions. They also result in increased healthcare efficiency through quick turnaround, at times before patients even leave the site of service, to help optimize the timing and administration of therapies, improve adherence to therapy, and help address the challenge of healthcare disparities especially in hardest hit populations.

They can also help resolve improved patient satisfaction, the reduced waiting times, reduced anxiety, and potential avoiding of unnecessary health interventions. They also can help result and improve utilization of healthcare services by shrinking waiting times in the emergency department and other near patient settings. And they can help move from traditional medicine to predictive and more personalized medicine through empowerment of patients and providers.

The diagnostic industry, through technological advances at the point-of-care, is helping to meet needs amidst increasing chronic and infectious disease, antibiotic resistance, and demand for access for all Americans to quality laboratory testing and convenient, timely healthcare. Given the rising incidence of diabetes and its healthcare impact, there is considerable opportunity to aid early and accurate identification and prompt, necessary intervention for patients.

In closing, AdvaMedDx encourages a wider dialogue on the importance of point-of-care diagnostics as we move to 21st century healthcare. Healthcare is evolving, and care is often decentralized. We should take care not to place hurtles to point-of-care interventions and to encourage access for innovative technologies. Near-patient testing is central to ensuring that all patients receive the best quality care and help curb the proliferation of undiagnosed diabetes for America's patients. As a significant public health issue, increased access to point-of-care tests, such as HbA1c tests, will have a positive impact on the diagnosis and management of diabetes. We should continue the progress being made and ensure that patients and healthcare professionals have the best possible tools available to them.

Thank you for the opportunity to comment today.

DR. WATSON: Thank you very much.

Are there any other audience members who would like to address the Panel?

(No response.)

DR. WATSON: Seeing none, I would close this portion.

I'd like to ask if any other members of the Panel have further questions of Dr. Ratner, because I believe he has to leave after lunch.

DR. HENDERSON: Would you consider being more comfortable if rather than a diagnosis of diabetes were made by this device at a A1c of 6.5, if there was a disclaimer that the -- it should be used as a screen if the A1c was between 6.4 and 6.6, because we've heard that the range matching up with the labs was about in that -- would that work for you?

DR. RATNER: No, it really wouldn't. And it goes back to Dr. Burr's comment. There really isn't a lot of difference there. The issue of diagnosis is a categorical issue. And it's a labeling issue that is the major problem that we have. And before we do that to an

individual, I believe we need to make sure that the quality of the test that's being done in the setting in which it's being done is most appropriate.

I want to address the issue of ascertainment of trying to find people with diabetes. The CDC for many years has talked about 20% of the people with diabetes not knowing they have it. And the issue of point-of-care testing and whether or not that's going to make a difference is entirely unknown. It hasn't been tested. What has been tested in a very interesting natural experiment is access.

So in a paper that came out in *Diabetes Care* this last year, Kaufman et al., looked at those states that expanded Medicaid versus those states that didn't expand Medicaid in terms of their ascertainment over a 6-month period of time for newly diagnosed diabetes. The entire study was done through quintiles, so a central laboratory with high-complexity oversight.

And what they found was compared to the control period of time before Medicaid expansion, those states that did not expand Medicaid had no change in the number of new individuals diagnosed with diabetes. In the states that expanded Medicaid -- so you now have access -- the ascertainment of newly diagnosed diabetes rose by 23%, almost precisely what the CDC had recognized as the undiagnosed.

The other interesting aspect there was that in the states that did not expand Medicaid, the average A1c at diagnosis was 8.6. In the states that did expand Medicaid, it was 7.2. So there really are substantial differences in diagnosis simply due to access.

DR. WATSON: Thank you.

Are there any further questions for --

(Off microphone comment.)

DR. WATSON: Technical -- there you go. No, don't touch it again.

DR. HENDERSON: Okay. Is that it?

DR. WATSON: No, don't touch it again.

DR. HENDERSON: Okay. Is it on? Okay.

My sense of what was your biggest concern were those -- the false positives, those individuals who did not have diabetes and they were labeled as such. But would not expanding the -- well, I understand there's a cutoff and it's an arbitrary cutoff, but at some point, wouldn't there be a benefit to getting more who are affected even if -- as you decrease the risk of the false positives by expanding it around 6.5?

DR. RATNER: The bigger problem is actually the false negatives.

DR. WATSON: Doctor --

DR. HENDERSON: (Off microphone) to identify some positives that you're missing, but to avoid the false negatives if you expand it around that 6.5?

DR. RATNER: I think that makes it even muddier in terms of the diagnostic criteria.

DR. WATSON: Can we have Dr. Lias?

DR. LIAS: Before you have to go, I do have one question. I've noticed a lot of times that sometimes terminology is something that's very confusing. So I think one of the things that's challenging to us is that our interpretation of the term "point-of-care" is broader than CLIA waiver. But can I ask you to clarify, when you say "point-of-care," do you mean just CLIA waiver -- CLIA-waived point-of-care labs, or do you mean point-of-care labs that are either CLIA waived or moderate complexity?

DR. RATNER: The distinction in our standards of care really centers on the proficiency testing, which would suggest that if it's a moderately complex point-of-care test, that the quality control is adequate. It's the absence of the proficiency testing that leads us to question the value of the tests themselves.

MS. McCOLLISTER-SLIPP: So, again, sort of looking at what they're -- Anna McCollister-Slipp. So what we're talking about today are basically two things. One is the

data they presented is based on this moderate-complexity environment with proficiency testing, with the possibility that at some later point they will want to expand that to CLIA waived. So I mean, the data they've suggested that I've seen, what I've seen looks as if like for this moderate-complexity indication, it's pretty consistent with what you see in the central labs. So that would seem to get beyond your concern about proficiency testing?

DR. RATNER: Correct.

MS. McCOLLISTER-SLIPP: Am I hearing that right?

DR. RATNER: Yes.

MS. McCOLLISTER-SLIPP: Okay. So your concerns -- and actually, I think -- I applaud ADA for having a very different perspective from the FDA. I think that's kind of your job. I think what FDA does and what ADA does are two completely different things, and I think there needs to not be -- I think that's healthy, so I just want to put that on the record as a patient. And I see that as being your job is to push things. But your concern is sort of the natural tendency of people like me in the world to take something that's been indicated for one thing and use it -- sort of logically extend that to another environment, which the Sponsor has indicated is something they might consider in the future?

DR. RATNER: That is our concern. Again, the concept of using a moderately complex test with appropriate proficiency testing, we have not had any objection to in terms of A1c for diagnosis. None.

DR. WATSON: Okay. We have Dr. Nipper, Dr. McShane, and then Dr. Rej.

DR. NIPPER: Yeah. Well, I just wanted to applaud Dr. Lias for asking the question again and clarifying the fact that the proficiency testing is the issue. The issue that I have now is in moving to -- this test which looks like it's going to work well in a moderately complex environment, move it to a waived environment without the proficiency testing looks like CLIA problem, not an FDA problem. And I'm concerned about that because there

are all sorts of other waived POC tests out there that may not meet the same criteria for quality performance. So I think the challenge we have from a regulatory environment, and you from the ADA's point of view, is how do we ensure quality testing out there if it were to be waived? And above all, do no harm, and I see Pandora's box yawning open, you know, beginning to yawn open out there.

DR. RATNER: I completely concur. That's our concern as well. It's why throughout my original presentation I actually italicized and changed the color of the font for proficiency testing throughout. I think the quality control is the critical issue here. And once we get into a CLIA-waived environment, we don't know, and that's the concern.

DR. WATSON: Thank you. Dr. McShane?

DR. McSHANE: Yeah. So just following up a little bit on that, I think it would still help to see data that would suggest whether or not this new test with all of its bells and whistles, you know, whether proficiency testing would actually make a difference or not.

But my sense, and people can certainly disagree with me, is that we're not actually talking about the test here. I think what we're talking about is if we were to require that the test, even a point-of-care test, be done in at least a moderate-complexity environment, to me that's kind of a surrogate for entering an environment where you're going to have reasonable healthcare expertise available. And I think this is what this is all about, you know?

In oncology, we have lots of tests out there that people do, and there's often a phrase that is put into the clearance statement that says this should be interpreted in the context of other factors, you know, with, you know, certified pathologists or whatever. And so I think that's really what we're talking about here, you know? We don't want a value out there -- whether it's been done under, you know, proficiency testing conditions or not, we don't want a test value floating out there without the assurance that there's

proper medical expertise to interpret it, decide -- you know, you've got a test on the borderline, and you see the person in front of you who's, you know, 100 pounds overweight, has a family history of diabetes, you know? You're going to make a different decision about interpreting that value than if -- you know, than just a naïve what side of the cut point does it fall on?

DR. RATNER: Then if you're at the supermarket doing a test --

DR. McSHANE: Yes, right. Supermarket, you get your number, you know, someone walks off with a number not knowing what to think of it. And I think we should really focus on what we are really trying to accomplish in getting an appropriate clearance statement if the device is ultimately cleared.

DR. WATSON: Okay. Dr. Lias and then Dr. Rej?

DR. LIAS: Mine is just a general clarification. I realize we may not have made clear the reason we're asking the CLIA question. It's because FDA has been deemed authority by CMS to actually make the decision on whether a device should be CLIA waived. So if that wasn't clear, I just wanted to make clear that if Alere or another company were to request CLIA waiver in the future, they would request it from us.

DR. WATSON: Thank you.

Dr. Rej?

DR. REJ: I appreciate -- this is Dr. Rej -- I appreciate the ADA's interest in high-quality laboratory results, but I was wondering if you could comment on data presented, I believe, by Dr. Scott showing that some of the analyzers which are aimed for central laboratories actually seem to perform less well than those that were aimed for the point-of-care. So I don't know if you have a comment on that?

DR. RATNER: So I have no specific expertise in terms of laboratory medicine. As a clinician and clinical researcher for 35 years, I depended upon quality labs to make clinical

judgments, to make research judgments.

From the standpoint of the American Diabetes Association, we do annual reviews of our standards of care for a reason. Science changes. And we are ready and willing to adapt to those scientific advancements.

If, in fact, the data are available to show that the waived devices are as good, if not better, than a moderate-complexity lab, we are very open to that possibility. We hope it occurs. To date, we have not seen that occur. As I said, I was not privy to the data from the Sponsor. We have not reviewed it. I can't make any comments on it. But clearly, if decisions are made within this Panel and subsequently by the FDA, the ADA will consider those and see whether or not they require changes in our standards of care.

As you saw from 2010 through 2016, the wording did change as more information became available. And we remain open-minded, and we will continue to make changes as necessary.

DR. WATSON: Thank you, Dr. Ratner.

One last question, then lunch.

DR. WYNE: Okay. This is Dr. Wyne speaking. You know, everybody keeps raising this concern about the CLIA-waived situation, and I applaud you guys for focusing on the proficiency aspect, in other words, is it being done scientifically correct? But then we keep taking it to the setting where that's going to happen, the community screening, the mall, the grocery store, whatever. I found it interesting that in FDA's presentation, their example of a setting with a certificate of waiver is actually a community health clinic.

So I would guess the community health clinic actually has the medical expertise to counsel and act on the results of the test. So it just kind of strikes me that the setting we've been focused on isn't the only setting where it's going to be potentially used in a CLIA-waived setting. And the issue that's been raised is the medical follow-up of the test if

it was done properly. We don't yet have the science to show that without the performance testing it can be done accurately and safely. And perhaps if that science came, the ADA would change their position.

So I think that we need to separate the science from the setting, and I almost think the community health center is a place where it could meet the ADA's medical concerns with a CLIA-waived test if it was scientifically valid.

DR. RATNER: I think your points are absolutely on target. So it's why I separated out A1c for diagnosis from point-of-care testing. In fact, I'm not as concerned with the community health center, the federally qualified health center where medical care is available in terms of the follow-up. Assuming that the quality of the test is there, that would be quite appropriate. They could also operate under a moderately complex laboratory, and then there's no problem at all.

When you have a waived test, then the applicability well outside of those healthcare settings becomes possible, and we are very concerned about the Lions Club doing a screening at the mall or those sorts of settings. And I will grant you, it is not limited to A1c. We are against that for glucose, as well. So, you know, the issues are really quite separate.

DR. WATSON: Okay. Thank you, Dr. Ratner. Thank you very much for staying. I appreciate that.

I think we'll break for lunch now. There will be -- the Sponsor will have a analyzer on the front desk for you to all see if you'd like. I'd like us all to come back here at 1 p.m. sharp.

Panel members, please do not discuss any of the comments or contents of today's deliberations amongst yourself or with others.

We'll see everybody at 1.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:07 p.m.)

DR. WATSON: So I'd like to call this meeting back to order. We are now going to continue on with public comments. And we have an additional commenter, Dr. Rendell, who will give public comments after we hear a description from Lieutenant Commander Garcia.

LCDR GARCIA: Thank you, Dr. Watson. Thank you. Can you hear me?

DR. WATSON: Um-hum.

LCDR GARCIA: Thank you, Dr. Watson.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Watson?

DR. WATSON: Dr. Rendell, please take the podium.

DR. RENDELL: It turned out that I was supposed to be on the Panel for this, and

then I was excluded from the Panel not because I have any relationship to the Sponsors but because, quite separately from anything that was going on at the FDA or with the Sponsors, I was doing research on this particular topic and published my work very recently.

So I'm Dr. Rendell. I'm from the Creighton Diabetes Center and the Rose Salter Medical Research Foundation.

And very recently, a decision was made to diagnose diabetes by a hemoglobin A1c value of 6.5. There are a variety of diagnostic approaches to try to make a diagnosis, both clinical and biochemical: random glucose values greater than 200 accompanied by symptoms and signs of diabetes; several random glucose values and glucose values on a glucose tolerance test above certain cut points; fasting glucose values greater than certain cut points. They all differ. And now hemoglobin A1c was introduced by the WHO and embraced by the American Diabetes Association.

So diagnosing diabetes by glucose. Well, to paraphrase a former President who has a conflict of interest with a current candidate, it all depends what you mean by glucose. Is it plasma glucose? Is it whole blood glucose? Is it fingerstick glucose? Is it 115 mg/dL or 120? Is it diabetes or pre-diabetes or impaired glucose tolerance or impaired fasting glucose? And, of course, all of these differ in pregnancy, where it is gestational diabetes.

The hemoglobin A1c definition was actually based on an epidemiologic correlation with retinopathy. It had nothing to do with laboratory medicine. It just turns out that on numerous epidemiologic studies, when you look at development of retinopathy, it seems to increase over a hemoglobin A1c of 6.5% in various studies, such as the DCCT. Well, what about hemoglobin A1c? It all depends what you mean by hemoglobin A1c. Is it HPLC? Is it affinity? Is it amino assay? Is it in percent or now milligrams per deciliter? And again, the definition correlated with retinopathy, not with glucose values.

Many years ago, because values were so discrepant and so unstandardized, a program called the National Glycohemoglobin Standardization Program, now known as NGSP, attempted to standardize all assays against the DCCT HPLC standard. And they maintain a pool to this day where they believe that they can go back to the original HPLC values that were obtained in the DCCT.

Well, everything was based on comparison of point-of-care, POC, with central laboratory values. And there was great disagreement about whether point-of-care was equivalent to central laboratory. But everything was based on single time points. And what we need since we actually treat patients is values that are invariant over time.

So we took the two most prominent point-of-care techniques, which were the Afinion and the DCA, with the two most prominent, most used central laboratory techniques, Bio-Rad and Tosoh. And we measured values over a 3-year time period in a very large patient population while following what is called the NGSP bias, which means how much do given assays -- although acceptable to the NGSP -- how much do they differ from the NGSP values over a certain time point? And, of course, what we found is that all of these correlated extremely well whether it be point-of-care versus central lab or, in fact, point-of-care versus point-of-care. Correlation doesn't mean accuracy.

And when we compared point-of-care to the two central laboratory values, there were differences. And there were differences over time. Actually, both point-of-care values, whether it was Afinion or DCA, differed from Tosoh by various amounts. I'm sorry this slide doesn't show up as well, but in fact, the point-of-cares were less than the Tosoh and the Bio-Rad values.

But when we then looked at bias, it turned out that there was significant bias, in fact, of the central laboratory procedures so that the Tosoh bias was systematically high by as much as 0.5%. The Bio-Rad bias varied very significantly. And, in fact, towards the end

of the study, the mid-range value correlating with hemoglobin A1c varied by about as much as 0.5%. When we looked at the point-of-cares, again, there was significant variation, but no more so than the central laboratory values.

So what we discovered is that the hemoglobin A1c bias from the so-proclaimed gold standard, HPLC, varied from -0.4 to 0.4%. The hemoglobin A1c bias with central lab, largely because Tosoh was systematically high, varied from 0.1% down to 0.5% up. And the bias values varied widely over the 3 years of our study, which, by the way, continues.

So, in summary, I would argue that point-of-care techniques are no worse than central laboratory assays for measurement of hemoglobin A1c. We have shown that over time, the variation from what one would consider the ideal is no different. And certainly it is questionable whether a single hemoglobin A1c measurement by any technique should be used to make a diagnosis of diabetes. The NGSP allows a variance of 0.3% from a given A1c value up or down. That is quite significant if you're going to attempt to label someone as having diabetes in terms of insurance purposes.

I'm pretty sure that the real decision here is whether point-of-care should be used and should be a perfectly reasonable substitute for central laboratory assays. I think our data shows that it should. Whether any of these should be considered as a diagnostic technique for diabetes, I would argue against.

Thank you. And I'll entertain questions if anyone has them.

DR. WATSON: Thank you.

Are there any questions from the Panel? Yes?

DR. REMALEY: I guess just a point of clarification, but the Tosoh, not to my understanding, is not considered -- you mentioned as a gold standard, but it's not truly a reference method. And I think that's part of the problem. Unlike in lipids, where it's true we have reference methods, we don't have a real anchor.

DR. RENDELL: There are reference methods. Tosoh, yeah, is not one of the NGSP so-called reference methods. However, you should be aware that the assays approved by the NGSP and that are in current use vary anywhere from immunoassay to affinity to HPLC. So whether one accepts the fact that they are reference assays or not, we have to come to the understanding that these assays are the conventionally used assays in central laboratories.

DR. WATSON: Thank you.

All right. If there are no other questions from the Panel, I would like to ask are there any other audience members who would like to give comment?

(No response.)

DR. WATSON: Hearing none, I now pronounce the Open Public Comment section closed.

So we'll now move on to deliberations from the Panel. Can we have the questions back up on the screen? We'll focus our deliberations now around these specific questions that we can give guidance to the FDA about. We've done a lot of discussion already, so we'll move from there.

Next slide, please? There we go. Okay. So the first question we're asked to consider, shown here, if you guys can read that to yourselves, and then we'll start deliberating (a).

(Pause.)

DR. WATSON: So the question really is does the Panel have any concerns about risks to health regarding the use of point-of-care hemoglobin A1c devices in general for the diagnosis of diabetes. Comments?

DR. LIAS: With a focus on point-of-care, not whether A1c should be used --

DR. WATSON: Exactly. Focus on point-of-care. Any general concerns about point-

of-care A1c diagnosis?

Doctor --

DR. WYNE: I would say from the discussion and the information I've seen so far, from a technical point of view, if a point-of-care test can meet the technical criteria, then it's an acceptable test for the diagnosis of diabetes.

DR. WATSON: Dr. Nipper?

DR. NIPPER: I'm okay with it as long as it's moderate complexity, and people then do PT and actually can show the PT agrees with consensus. If you don't do PT, I don't want to give that a green light.

DR. WATSON: So we hear that point-of-care testing as long as proficiency testing is included is probably acceptable to this Panel; is that correct?

MS. McCOLLISTER-SLIPP: I would like to say that, I mean, we've been given data about use in the moderate-complexity environment, so including the proficiency testing. Knowing that things tend to migrate once a diagnosis, you know, a particular indication has been granted, I think it'd be really helpful -- whether or not you make this a condition of whether or not this approved is a different question, but I think it would be very helpful to see how this test performs by people who are not in that kind of an environment.

DR. WATSON: Sorry. I do think that will come into play when we answer Question No. 3.

MS. McCOLLISTER-SLIPP: Okay. Sorry.

DR. WATSON: So let's discuss. So I think in terms of Question 1(a), we can summarize by saying the Panel has no concerns about risks of health regarding use of point-of-care hemoglobin A1c testing as long as proficiency testing and all the other checks and balances are put into place.

Is that correct?

MS. McCOLLISTER-SLIPP: Well, for this device. I mean, we've seen good data for this device.

DR. WATSON: We're not -- okay. So this question doesn't ask about device specificity. It's about general point-of-care hemoglobin A1c devices.

DR. WYNE: So, in other words, if technically it meets what's needed to make the diagnosis, are you okay with having a point-of-care device in your clinic to make the diagnosis as opposed to having to send it out to a lab? That's the question.

DR. WATSON: You had a comment, Dr. Burr?

DR. BURR: Yeah. Remember, the machine doesn't make the diagnosis, you know? You know, I've never had one that has a little red light that goes off on top that all of the sudden it says, oh, somebody has diabetes. The diagnosis is made by somebody who's interpreting the lab result. And that's like any other lab result. So the question for me is whether or not the machine provides an accurate result, which in my experience it does.

My concern is that if somehow by accident this moves from CLIA waived to moderate complexity, most offices that do the testing will lose the ability to do that because moderate complexity is much more expensive and simply prices it out of -- I realize we're not supposed to deal with cost --

DR. WATSON: Yeah.

DR. BURR: -- but I'm saying that that will be a consequence.

DR. WATSON: Well, but the -- Dr. Lias?

DR. LIAS: You know, the clearance of this assay as a moderate-complexity version does not remove the clearance of the CLIA-waived version for monitoring.

DR. WATSON: Right.

DR. LIAS: The Sponsor tells us that they plan to have two versions.

DR. BURR: Right. There's been lots of discussion about the level at which it ought

to be done, and it's hard to avoid at least a concern that if it were reclassified, that its access to most offices would actually disappear.

DR. WATSON: So this is not about reclassifying at all. It's going to be a separate device and indication.

DR. BURR: Okay.

DR. WATSON: Okay. Have we captured -- oh, I'm sorry, I'm sorry. Go ahead.

DR. REJ: Yeah, this is Bob Rej. I think we heard earlier this morning there's point-of-care and point-of-care. And I think that the ADA representative would have no problem with a health clinical that's a standing -- perhaps associated with a parent facility. But the specific example, the Lions Club bringing a device from place to place -- so it's not so much the device, but I think the setting. So even though we say point-of-care, but we're largely talking about, in many cases, waived devices, and in some cases now reclassifying something to a moderately complex or a new submission of a very similar device as moderately complex.

But in the slide from the FDA, it says that the difference between moderate complexity and certificate of waiver is a requirement for proficiency testing. That's true for those analytes that are specified in the *Federal Register*. And hemoglobin A1c is not one of them. So a laboratory that's running a moderately complex device and is moderately complex has an alternate strategy to demonstrate accuracy, which could be more rigorous or less rigorous than participation in a proficiency testing program.

DR. WATSON: Do you have a comment about that from the FDA?

DR. LIAS: That's true.

(Laughter.)

DR. REJ: Thank you.

DR. WATSON: So we have been focusing on proficiency testing, but as you point

out and you verify, there are other --

DR. LIAS: So they still have to do two times a year some assessment. I don't know if you want to clarify that?

DR. REJ: Yeah. I believe the CMS was verification of accuracy in lieu of proficiency testing, but again, that can be very rigorous, or it could just be have technician 1 run it and then technician 2 run it the next time, and that's my validation of accuracy.

DR. WATSON: Good point.

Yes?

MS. McCOLLISTER-SLIPP: I sort of have two minds about this, and probably more than that. I mean, on the one hand, I feel like, you know, we want to make sure if somebody is being diagnosed and it's going on their record that -- you know, if they're going to have life insurance issues, then that's a problem. And it is a real problem.

On the other hand, I feel like -- you know, I keep thinking back to when, in the HIV world, when they were questioning whether or not people could handle the settings in which you could do like HIV testing. And I knew a lot of people who wouldn't get tested because they didn't want that to be on their record. And as a result -- I mean, I know it's an infectious disease and there are lots of differences, but I think knowledge is power. And the more people know, regardless of what setting it ends up in, I think the better off they're going to be.

So my bias is always to let new technologies go if there's a reasonable risk that it's not going to endanger somebody. My tendency is to think that that's the case with this particular kind of a device. But again, it would -- it really depends less on what happens here than it does about the implications of other elements that aren't under FDA's jurisdiction.

DR. WATSON: Yes.

DR. HENDERSON: I'm not sure which question this answers, but over the day, I'm not concerned about the use of this device in any setting. I think if it indicates -- if a patient gets -- not a patient -- a person at the Lions Club gets a A1c of 2.7, I think likely they're going to see somebody and ask about it. But I also think that if they have diabetes, it will percolate and somebody else will see that. I don't think anybody who would come to me and say that they had a 6.7 A1c and they want to be treated for diabetes, I wouldn't do that. I mean, I would work them up, and I would evaluate them and see if they have it or not. So the negative of somebody having it and getting labeled would not happen in an urban setting or a church screening in the basement. That would only come when it comes to light into the healthcare -- you know, in a healthcare setting, which means that they get treated if they have it. And if they don't have it, then we allay those fears, and we tell them whatever, they didn't wash their hands when they did the A1c, or whatever it is. But I really don't see that there's a risk or hazard wherever this device is used.

DR. WATSON: Okay. So to summarize again, I think, in general, we don't have concerns about this, but we do know that there's a separate piece, including how exactly rigorous the proficiency testing, or whatever, is done and how the information is used by the consumer, the patient, when they get it, and is there any healthcare provider or context that they can then share it with?

Is that a fair assessment guys?

MS. McCOLLISTER-SLIPP: Yeah. I would say that I'm less concerned about what the consumer will actually do with the information. I think more information is better, and it's helpful to have more information at the point of which you're actually seeing a doctor, so --

DR. WATSON: Okay. Good. Thank you. All right.

DR. NIPPER: This is Nipper again. I think that the other piece that we haven't

talked about is the ADA recommendation that a diagnosis not be made unless there are two sequential A1c values that --

DR. WYNE: No, two separate tests.

DR. NIPPER: Two separate tests.

DR. WYNE: Two separate tests.

DR. NIPPER: Yeah, two separate tests.

DR. WATSON: On different days.

DR. NIPPER: Yeah, on different days. And so I think it's important to -- it might be important to think about that in terms of Dr. Burr's concerns about having this test done in a clinical environment, or the result being then evaluated in a clinical environment and an appropriate follow-up test be done if the test calls for such.

DR. WATSON: Right, yeah. And I think that's implicit in what Dr. Burr said, so we're --

DR. NIPPER: Yeah. This is not just a number that automatically --

DR. WATSON: Right. And that's I think why we sort of have -- also some of our members have concerns that --

DR. NIPPER: Right.

DR. WATSON: -- it be in the context of clinical care.

Yes?

DR. WYNE: I mean, my concern is exactly what Dr. Nipper had mentioned of the test. If it's technically good, as long as it has the proper controls, yes, it's a good test. But then you guys are moving on to the context of the test. And what was mentioned earlier is in the screening setting, patients do not act on the results. They do not take that piece of paper and go to their primary care and say I need to be retested. We know that.

MS. McCOLLISTER-SLIPP: I don't know if that's true.

DR. WYNE: No, we know that.

MS. McCOLLISTER-SLIPP: We do?

DR. WYNE: Yes, we do, whether it's a fingerstick glucose or something else. And many of the people who go and get screened at the health fairs know they have diabetes, know that they are not under treatment. They're just curious to see how uncontrolled they are that day. So Dr. Ratner's concern about having a way to follow up on the test is a very valid concern.

Here's the other thing. As he said, what's your number one risk factor for type 2 diabetes? Family history. So you know you're at risk for diabetes. And you hear on the news every day the things you need to do to try to prevent it. People know their risk. They have the option to go on the ADA website and actually, you know, calculate their risk. The issue is what do people do with the information once they're given it, and the assumption is that in the healthcare setting, an action will be taken. An action is not always taken.

I cannot tell you how many times I've pulled up someone's labs and said, well, you know, your A1c was 6.7, 3 years ago, but you're telling me you do not have a history of diabetes, young patients who tell me they passed their gestational diabetes screen and they failed it every time. So, you know, the healthcare system is not perfect, but the ADA's concern of what's going to be done with that information is valid because we don't know if that A1c of 6.7 is going to be 6.4 in 6 months or 9.5 in 6 months.

DR. WATSON: Right, but that is not, I guess, particular to this point-of-care testing.

DR. WYNE: And that's actually my point is that's not what we're here to talk about, how is the information dealt with. But that's part of why the ADA has that concern of what's going to happen with the information. And unfortunately, the action that you want to believe is going to happen isn't what usually happens.

DR. WATSON: So let's try to move back. So I think we've kind of clarified 1a.

Let's move to 1b: Does the Afinion HbA1c Dx test system, with an intended use in moderate complexity POC service settings, raise any new concerns about risks to health? And if so, please describe.

Discussion? I see a bunch of head nods saying no.

All right. So I'm going to summarize our feelings on 1b as nobody has -- oh --

DR. REJ: This is Bob Rej. I don't have a concern, but I think that a moderate-complexity setting, regardless of the classification of the device, would probably be more comfortable with the ADA. That's more likely --

DR. WATSON: Correct.

DR. REJ: That's more likely to be a setting where there will be --

DR. WATSON: That's what Dr. Ratner said.

DR. REJ: Where there will be follow-up and necessary counseling and recommendation for retesting.

DR. WATSON: Okay. So we, as a Panel, feel comfortable saying we have no concerns about (b). No concerns, correct, as a Panel?

(No response.)

DR. WATSON: Okay. So let's move to 1c. Oh, we can do this one easily. If the Panel has concerns -- we have none, so we can go down to Question 2.

So everybody can read through the base and then we can ask the question.

(Pause.)

DR. WATSON: Actually, I would like a little bit of discussion about the base, so does everybody accept that premise as true, saying that people in the community will know that both systems do the same thing, so one will be used as their Dx and not the other?

DR. WYNE: I would argue that the person who does the ordering or the person

who's in charge of "running labs" in whatever setting will know there's a difference, but the person poking the finger and running the test probably is not going to know there's a difference.

DR. WATSON: Right. I think they're saying, though, when the two devices are essentially the same, the clinician knows that, that they might use the one meant for monitoring to make a diagnosis and maybe -- I don't know.

Is that what you're basically saying? Yes?

DR. LIAS: I think the question is whether there is a concern with that, if you, you know, if you believe that would happen or not, and if their strategy would mitigate any concern, if there is a concern.

DR. WATSON: Did you have a comment?

DR. HENDERSON: I don't have any concerns about it because it's the same machine, so I mean, from what I've seen, it's the same. And I think it would function the same. And if it's okay for a waiver, then it should be okay. I mean, the question about diagnosing with A1c, that's a whole nother issue that has nothing to do with it.

DR. WATSON: And then --

DR. HENDERSON: But the other thing, I think, yes, the clinician will know, and the only reason I think it would make a difference is if the price point is different, and that's why I can't ask. So if it's the same machine, I think that it would be fine.

DR. WATSON: Right. But what would be different is the proficiency testing would not happen.

DR. HENDERSON: I understand that, but the clinician would be the same person running the testing in the lab. I mean, it depends on which machine they had bought. And so if -- and it's the same machine, so --

DR. WATSON: It's the same machine.

DR. HENDERSON: Yeah.

DR. LIAS: So I want to clarify that the CLIA waiver assessment that was performed for the machine was for the other claim.

DR. WATSON: Right.

DR. LIAS: So it has not been assessed for accuracy around the decision points for this claim or whether not the failsafe mechanisms or its design would be appropriate for CLIA waiver for this claim. That has not been done. And the way that that waiver was done is a little bit different than the way that the waiver would be done for this particular thing, so that hasn't been assessed, so --

DR. WATSON: Right.

DR. LIAS: -- you know, I just wanted to clarify that.

DR. WATSON: Right.

Yes?

DR. WYNE: So I have a question related to that that I've not been sure I wanted to ask this question. As an endocrinologist, when I make a new diagnosis of diabetes, it's probably most commonly on the criteria of elevated glucose with symptoms. Meaning when I'm making a diagnosis, it's most commonly a sugar of 350, polyuria, polydipsia. But do we know if in general practice, whether it's general internal medicine or endocrine, are people using their using their current point-of-care monitoring machine to make the diagnosis? Do we have any knowledge of what's being done? I mean, I can tell you I'm not doing it, but I'm also in an academic tertiary care center, so --

DR. WATSON: I can tell you it's not FDA approved for that, so I don't know that the FDA would have any statistics on that.

Do you guys?

DR. REMALEY: I don't have the answer to that, but I think that it's likely that there's

off-label use for this indication, and I think what the manufacturer has done alleviates my concerns about the confusion effect. It may have some benefit, because those people who are using off-label will now realize, oh, it's not approved for that, and I really need to up my level of, you know, compliance in terms of proficiency testing. So it may have actually a benefit to the community. But this is just a theory.

MS. McCOLLISTER-SLIPP: And it sounded like, you know, ordering codes -- and this is a little unclear to me, so please, whomever, tell me if I'm wrong -- it sounded like you couldn't even order like the diagnostic cassette without -- and then make a claim for diagnosis based on the ordering codes --

DR. WATSON: Right.

MS. McCOLLISTER-SLIPP: They would still use the monitoring cassettes. But then there are some clinicians who would then make a diagnosis with the monitoring cassette, is the thought? I don't --

DR. WYNE: So it's like the same thing if I make the diagnosis off a fingerstick of 350. The fingerstick glucose meter is not approved for the diagnosis of diabetes, but if the meter tells me they're 350 with symptoms, I'm confident they have diabetes, and I'm going to send their blood to the lab to find out their baseline A1c. That's not for the diagnosis. I've already made the diagnosis. But I'm just curious if in general practice people are just using the machine they have in their office. Even though it's only approved for monitoring of intra-individual trends, are they actually using it for diagnosis? I don't know that answer.

DR. BURR: I do. Of course they are, you know? That's why this whole thing is silly basically. I mean, it's just --

DR. WATSON: They're already doing this is what you're saying?

DR. BURR: Yeah, yeah. I mean, it's the same machine. It's got the same results.

It's going to provide the same data that will inform diagnosis making, which it informs now, whether it's, you know, on-label or off.

DR. WATSON: So I guess we can then focus on the second part. The Sponsor did give us several things that they thought could mitigate that risk, and do we feel that those were adequate to address this concern?

DR. HENDERSON: It's a concern. I just think that the test -- if we believe this machine does what -- it seems to have done it without any adverse reporting events. It gives you a number, and then you use that number clinically to manage the patients. If you're going to use the number to make a diagnosis, that's, you know, off-label. But in the one test -- one unit that's there now, you use it to screen and to manage the patient, but it's the same test. You're going to get the same number, but now you're going to use it to make a diagnosis. I don't know that -- I mean, they've had these things that show how -- make sure they're using each machine for what it's approved for, but I don't think that there's a concern because it's the same machine, and it's giving you a number, and you're going to use the number in whichever setting you need it.

DR. WATSON: Dr. Wyne?

DR. WYNE: So my answer to this would be no, that the things they're doing to mitigate do not resolve the concerns because the concerns don't have to do with whether or not the machine says this test is approved for diagnosis or this is approved for monitoring. Our concerns have to do with what lab does it, whether or not they're doing the appropriate performance test and so on. So it's not addressed by what they've talked about because our concerns are not those issues.

DR. WATSON: I think I understand what you're saying.

Any other comments? I'm sorry.

DR. REMALEY: I just have maybe a question for the FDA. Again, perhaps we can't

discuss this, but is there a reimbursement difference in terms of diagnosis and monitoring?

DR. WATSON: I think we can't discuss this.

DR. REMALEY: Because if there were --

DR. WATSON: We can't discuss it.

DR. REMALEY: But if there were --

DR. LIAS: I don't know the answer anyway.

DR. REMALEY: Yeah. Could I --

DR. WATSON: Yeah, we can't discuss it.

DR. BURR: I can answer it if you want me to but --

DR. WATSON: We can't discuss it --

MS. McCOLLISTER-SLIPP: But it is relevant to the question at hand because we're talking about why somebody would choose one versus the other.

DR. WATSON: Okay. So we have to decide things without considering cost, and I've been told that many times by my FDA colleagues.

DR. REMALEY: But if you were using it for a diagnosis and they're using an unapproved test, it seems to me you can't get -- you shouldn't be able to get reimbursed for that. It may be the same test, but you're not doing the proficiency test, you don't have the moderate complexity of the lab, and then you should not be able to get reimbursed for that because you're not doing the appropriate test.

DR. WATSON: Yeah, and we don't have any concern --

DR. REMALEY: So that's why I asked. Not the difference of amount.

DR. LIAS: So we mentioned in our presentation very briefly that, you know, if a CLIA-waived facility was inspected by CMS, they would be cited for this.

DR. WATSON: Um-hum.

DR. LIAS: But very few of them are inspected, so it's really not a --

DR. HENDERSON: Risk.

DR. LIAS: Not a very high risk that they will be found out. But at the end of the day, FDA is concerned about health risks and risks to public health.

DR. WATSON: Yeah.

DR. LIAS: So, you know, certainly, we have labels and we have claims. But what we -- you know, what's also helpful to hear from the Panel is concerns, too.

DR. WATSON: My feeling about it is all of the mitigating strategies that you discussed are reasonable, and they would make sure that no one would accidentally confuse monitoring for Dx, but I don't think it's going to be an accidental thing if it happens, and they're easily overridden if you really want to, so --

MS. McCOLLISTER-SLIPP: I completely agree with that. I mean, I thought that they had used some clever uses of, you know, the way they designed the cartridge, or whatever, to be able to mitigate for those concerns. But the question is, it's like you say perfectly, it's not an issue of accidental; it's whether it's intentional.

DR. WATSON: So did we answer that question for you?

DR. LIAS: Yes. I think the question is answered, but I just want to make sure and confirm whether or not the Panel believes there are any risks introduced by intentional that we should consider. It sounds like no --

DR. WATSON: Yeah, well, that's a great question. Let's --

DR. LIAS: -- but I just want to confirm that.

DR. WATSON: Let's take a name poll. Can we have yes/no? Anybody?

DR. WYNE: So your question is are we concerned about the risks of the --

DR. WATSON: Let's assume people are going to use it off-label and use the CLIA-waived test to make a diagnosis. Are we concerned if that happens?

DR. WYNE: So --

DR. NIPPER: For this device?

DR. WATSON: For this device.

DR. WYNE: For this device as approved for Dx?

DR. WATSON: No, for this device as approved for monitoring. Are we concerned about the safety if people use it for Dx; is that correct?

DR. LIAS: If this were cleared, then there'd be the two versions.

DR. WYNE: Okay. So if this is approved as a CLIA-waived test, are we concerned about the risks of it being used to make the diagnosis? And I would say, yes, all of the concerns that were expressed by the American Diabetes Association are still out there and on the table, and where and how it's going to be used, and what's going to be done with the information. Technically, it may be an accurate test. We don't actually have the data of whether or not it stays technically accurate in the CLIA-waived setting. Nobody has given us that data. But the risks of giving the information to the person in the settings that were described has not been mitigated by what's done to prove its CLIA -- you know, to get the -- to show the setting. So I think all of our concerns are still there. They're not resolved by these technical things, and they're not something that we can resolve here.

DR. NIPPER: This is Dr. Nipper. I agree with Dr. Wyne. For the rest of the Panel, my opinion is that there's a reason that quality control procedures are done on high-complexity -- or moderate-complexity tests. There's a reason you do proficiency testing to assure yourself that your laboratory is doing the moderate-complexity test in a patient-safe manner. If you abandon that and use -- if one abandons the need for PT and QC and runs a waived test, then you are saying to yourself that it doesn't matter whether my test is right or wrong if the patient is not going to be hurt by a wrong answer. And I don't think that we can in good conscience say that about this particular test. You know, you may have great confidence in yourself and your lab and the way the lab is running the waived

test, but as I understand the law, you're saying that no damage is going to come to the patient from having a wrong answer on this test.

DR. WATSON: Dr. Henderson?

DR. HENDERSON: I think that clearly we're worried about wrong answers and damages to patients, but I just think that this in a waived setting is no worse than some of the labs that we use that we rely on and maybe even hold up as gold standards. I think, again, I think either if it's -- if it's less than 6.5 or more than 6.5, it's the whole patient, and it's just another piece of information. And if you can get this information more easily, I think you have to rely on it just like on all lab results or even clinical labs. If it doesn't make sense with the clinical -- with the patient, what you're seeing, then you repeat it.

DR. WATSON: Any other comments?

MS. McCOLLISTER-SLIPP: I just have to say, I mean, this gives me yet another reason to really not like hemoglobin A1c as a biomarker for diabetes, and I actually thought this might be a good use for it. I find it completely useless in type 1. But I think that's one of the things that we're struggling with because we've got this binary marker that, you know, taken completely out of context isn't really that helpful, but even if the physician takes it in context, the rest of society pools that information and uses it to make decisions that do have very significant implications for people.

So, I mean, and again, I'm thinking about this. I have a husband and a brother-in-law who are hovering right between like 6.4 and 6.6, and one feels great because he made it to 6.4, and one is at 6.6 and feels like crap. That doesn't matter. I mean, I don't see a difference between the two. So what is a risk? The risk is one feels a little bit bummed. Well, he's now like sending me his blood sugars every day. I mean, that's not that big of a risk on the one hand, but the issue is that these are binary measures and that I just don't think that that's really a great way of assessing one's health. Unfortunately, people like

numbers, and they like to assign value to numbers that goes far beyond the actual context in which those numbers were collected or observed. And I feel like that's the real issue here.

DR. WATSON: Okay. So I can tell there's a divergence of opinions here. So I was just asking if it was okay to informally poll the Panel, and I was told no. So I will not do that. But I do feel like this is going to be a divergence of opinions.

DR. WYNE: I don't think we're disagreeing with Dr. Henderson, and we're not saying that people are not going to do off-label fingerstick glucose or A1c to make a diagnosis. But again, you're describing in a healthcare setting, where there's support for the information and how is the information going to be used, and the concern is not when you're with a patient in that setting. The concern is all the other places. And so part of it's the scientific quality and part of it's a medical issue.

DR. WATSON: So I got a clarification. I am allowed to poll the Panel, but I have to make a summarizing statement at the end.

So I would actually like to informally poll the Panel on the question if you have concerns about the use of a point-of-care hemoglobin A1c test to diagnosis diabetes in a CLIA-waived setting, please say yes. If you have no concerns, please say no.

DR. LIAS: Well, that's Question No. 3. Are you planning to move on to that?

DR. WATSON: Oh, yes.

DR. LIAS: But if you're still talking about Panel Question 2, I mean, I think the distinction here is that, right now, this test is out there and waived for monitoring and can be used off-label. So I think the question is more about if this is cleared for diagnosis and everybody knows it's the same test, does that introduce any new questions that weren't -- that need to be addressed? And so that's the only question is --

DR. WATSON: Okay. And so that's a good clarification.

DR. LIAS: Should we address anything or not.

DR. WATSON: The clarification is not if it's out there and used, but the question is if we now have a FDA-approved Dx test --

UNIDENTIFIED SPEAKER: Version.

DR. WATSON: Version, does that introduce any new concerns or not? I say no, but what do you Panel members think? Are there any new concerns?

UNIDENTIFIED SPEAKER: Just go around.

DR. WATSON: Okay. Dr. Henderson?

DR. HENDERSON: No.

DR. WATSON: No? Dr. Nipper?

DR. NIPPER: No.

DR. WATSON: Okay.

DR. WYNE: My answer is no, but I like the fact that it actually brings increased knowledge and education about the issue. I think the off-label use will continue.

DR. WATSON: Okay.

DR. McSHANE: No.

UNIDENTIFIED SPEAKER: No.

DR. WATSON: No? No? Any concern?

UNIDENTIFIED SPEAKER: No.

DR. WATSON: No concerns?

MS. McCOLLISTER-SLIPP: Risks to immediate health, no, but I do think, you know, if it hasn't been cleared for that, there are implications of a diagnosis in some settings, but that's not FDA's job. Unfortunately, FDA's decisions do have impact in many other ways.

DR. WATSON: Okay. So no? No? Unanimously no.

Okay. So let's move on to Question 3. So based on the design of the Afinion

Hemoglobin A1c Dx test system:

a. Please discuss the potential advantages and disadvantages of using this test as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes in a CLIA-waived point-of-care setting.

So this is --

DR. BURR: Isn't that what's being done now?

DR. WATSON: It --

DR. NIPPER: You're talking about the Dx test, right, not the --

DR. WATSON: The Dx test.

DR. NIPPER: Yeah.

DR. WATSON: Which is identical to the current CLIA-waived setting.

DR. BURR: So that's what's being done now.

DR. LIAS: No, this is a question of whether they get this version cleared, this moderate-complexity version now that would have some sort of requirement for PT-like things, if not a mandated PT program requirement from CMS, and if they were to later come in and request waiver, and then it would be authorized for use in waived labs --

DR. WATSON: Which is --

DR. LIAS: -- as a point-of-care test for diagnosis of diabetes with that claim.

DR. WATSON: Which is what we believe is currently occurring in clinical settings; is that correct?

DR. BURR: Yes.

DR. LIAS: But the CLIA-waived version, if a laboratory were to use that for diagnosis, that any off-label use is actually, by default, high complexity, so they would get cited by CLIA if they were to be inspected as being in violation of CLIA by doing that. So if

they had a CLIA waiver for this test, then that would be on-label use, and CLIA-waived facilities would be authorized to use that test for diagnosis under CLIA.

DR. BURR: Explain for a minute how you link the use of a point-of-care A1c machine to the diagnosis of diabetes?

DR. HENDERSON: How would they know?

DR. LIAS: They may not know. This is a question for CLIA, so --

DR. HENDERSON: I imagine -- they don't inspect, but even if they came and inspected, how would they know that?

DR. WYNE: But the answer is how you do your logging, your documentation, and actually, with electronical medical records, it's very easy to determine that, and that's one of the things I've been thinking is our chart auditors, if they knew to look for it, then they would know to tell me that the machine I use in one of my clinics cannot be used for diagnosis. Therefore, I did not actually make the diagnosis, and I cannot get reimbursed for a Level 5 visit there because I didn't do that, so --

DR. BURR: You can make a diagnosis any way you want --

DR. LIAS: Our question today is not about whether the CLIA regulations are adequate to cover CLIA-waived testing. You know, the scenario that we're asking about is that you heard from the ADA today that they're concerned about using point-of-care diagnostic tests, sounds like in CLIA-waived settings for the diagnosis of diabetes, and their clinical guidelines recommend against it.

So if a company -- in this case maybe Alere, maybe someone else -- were to come to us with a test for a diagnosis claim and seek a CLIA-waived designation for that test, what should FDA consider in making that decision for whether we should authorize CLIA waiver? Are there things that should -- so the question is meant to get at what's the underlying concerns, and should anything be done by the Sponsor to mitigate the risks that are the

underlying concern of ADA, if you agree with those. So, I mean, some of it is about I think whether or not you believe that the risks that ADA is concerned about should be addressed or not, and if so, how.

MS. McCOLLISTER-SLIPP: From my perspective, I would like to see data on people who are not trained and whatever training that goes into the moderate-complexity environment, if the people are not trained, how they use it, and sort of see if there's a difference between how -- you know, whether somebody like who isn't trained does it versus somebody who is trained.

And then secondly, I think -- I mean, it's diagnosis, but I mean, I think there needs to be some sort of a guidance about the limitations; this should not -- this is a diagnostic tool, but it should not be entered -- it needs confirming, so that without a confirmation, then it would not be considered a valid diagnosis, which seems to be consistent with what ADA is saying anyway, that they want two tests.

DR. WATSON: Alan?

DR. REMALEY: Yeah. I think just to put our discussion in perspective, if I'm correct, there's CLIA-waived tests for coagulation testing, CLIA-waived tests for lipid testing. In both those instances, we use that to make therapeutic decisions. And I'm not saying it's good or bad, but I'm saying that currently exists. And so now we're asking whether we can potentially have the CLIA-waived tests for a diagnostic --

DR. LIAS: Particularly because the ADA has said not to do it.

DR. REMALEY: Yeah, yes, I understand, yeah. So I think if it can be done accurately, you know, I say why not, if the technology improves. And I think we currently have CLIA-waived tests which are perhaps more problematic, in my opinion, and they're currently CLIA waived. So I think we need to put that in perspective when we think about using this in the future.

DR. LIAS: So one question: I think it sounds to me like the ADA's concern is ongoing quality because of the proficiency testing, so if the Panel could comment on that and whether or not there would be ways to mitigate the underlying concern of ADA, if you believe it's necessary to do so?

DR. WATSON: So as far as I could tell, the ADA's position is based on expert opinion, and there is sort of a data void. And having been on guideline writing committees, those are the toughest things to break, expert opinion, because people get entrenched. So I don't know if there's any evidence or research that would change that. Does anyone else have a feel for that?

DR. NIPPER: This is Nipper. I can't comment directly on that, but I do have an opinion about whether or not a waived test should automatically just go over and be used for diagnostic purposes when A1c is involved. I think we've seen a situation where you have a couple of tests that perform very well from a precision and accuracy standpoint against well-entrenched laboratory tests. We don't have data on other waived tests that might also be used for diagnostic purposes for diagnosing diabetes with A1c.

So I'm concerned about, in general, lot-to-lot variability, making sure that that's within certain standards and guidelines and the ability for people to change over those lots and not have dramatic shifts in the answers. Not all laboratory tests are created equal. Not all laboratory tests for A1c are created equal, as you've seen from the publications where six of eight were not satisfactory.

So I think that there -- my concern would be if guidance is followed to make sure that the manufacturer quality and the performance quality is good, then I have less concern about waived tests being used for diagnostic purposes. But I don't know whether the market will take care of that or not, but I think the regulators need to be very watchful over manufacturing quality and performance quality over time.

DR. WATSON: I don't know. May I make a question to the Sponsor? I thought we saw data that showed about 30% of CLIA-waived and 30% of non-CLIA-waived tests were inaccurate. Is that correct?

DR. SAN GEORGE: Yeah. So, you know, we've talked about the data void. There are not a lot of data, but there are some data. So if I can summarize quickly, again, we saw some data in several pediatric GP practices in the U.S. that showed that two systems, Afinion and DCA, performed just fine. We saw a lot of data from Europe, from EQA programs in Norway, Sweden, and Switzerland, hundreds, maybe even thousands of GP offices, sort of like CLIA-waived settings here, not exactly, but a lot closer than hospital labs, and we saw that, in general, the data there, from those settings in the PT or QA programs there, show that the point-of-care systems mostly, again, DCA and Afinion, performed well and as good as the hospital systems that were used in those studies, as well.

DR. WATSON: And it was about 30%?

DR. SAN GEORGE: There were 30% that didn't perform up, but that was the same as the hospital. So 70% did point-of-care, 70% of hospitals did, and 30% did not.

Mitch, you want to comment?

DR. SCOTT: Yeah. One of my friends from Norway is sitting over here explaining the reason that both the point-of-care and the central labs had only a 70% pass rate in that particular survey in Norway. The criteria for acceptance in Norway is 100% successful. The criteria for acceptable in the CAP surveys is two out of three, or 67%.

DR. WATSON: Gotcha. Thank you. That's very useful.

Dr. Kwong?

DR. KWONG: I think one of the advantages or importance of having PT is you know where your laboratory is. And if 30% of a laboratory that participated in PT failed -- I'm in

New York. My regulator, Dr. Rej, will come after me. But if you don't participate in a PT program, then those 30% of laboratory that fail according to the data, they wouldn't know.

DR. SCOTT: I just want to drive this point home one more time. Failure in Norway is anything less than 100% successful.

DR. WATSON: Anything less than perfection.

DR. SCOTT: Failure -- yeah. So you have to pass on every sample. Failure in the U.S. proficiency testing per CAP is -- or successful is two out of three. So you can pass your CAP PT program by having the correct answers 67% of the time. In Norway, you can only pass if your results are correct 100% of the time. It's a big difference.

DR. WATSON: Okay.

DR. KWONG: Yes. I think the point I'm trying to make is if you do not participate in a PT program, you wouldn't know that you were out. That's all I'm saying.

DR. WATSON: Ms. Daigle?

MS. DAIGLE: Okay. I get very nervous when I speak, so my heart palpitates. Anyway, so this is my perspective of it from a consumer. The point (a), the potential advantage, I think there's great advantage for the consumer because healthcare is in a shift of paradigm right now, and there's less doctors. There's going to be less doctors in the future. There's less clinicians. So I applaud the FDA for looking at changes of standard of care and with valid scientific testing.

And my concern is not so much -- and I shouldn't say this -- but labeling as it is targeting the population and getting early diagnosis and treatment. And from a healthcare perspective, if you get them and you're a clinician, and you can validate that they have diabetes, even if they don't seek help right away, coming from a healthcare perspective versus a layperson's or family history that they know, it helps to put the seed in their mind that they need to seek healthcare. And the earlier the prevention that you have, the

better quality of life you have and the less comorbidities will come in the future. So you're actually helping the patients.

DR. WATSON: Thank you.

MS. McCOLLISTER-SLIPP: And I have to say that, you know, that's my bias, as well, in many respects. I mean, it feels to me like what we're deciding is whether or not it's possible to have something that could be used to diagnose diabetes that is relevant that is not within the sort of classic structure of the healthcare system. And that structure hasn't really worked all that well in dealing with type 2 diabetes or type 1 diabetes. And I don't think that we need to pretend that keeping people in that particular setting is necessarily the only way that people can get healthy, particularly when you're at the margins of developing type 2. Is it ideal that you get care from an endocrinologist or diabetologist or nurse educator? Absolutely. But we're far from ideal. And for something like type 2, there are things you can do that you can find out outside of the healthcare setting that would actually inform your ability to prevent it. And I'm not saying this is ideal, but that's the reality, and to pretend that people can't start thinking through this on their own I think is selling individuals short.

DR. WATSON: Okay. I have Dr. Wyne, then Dr. Rej.

DR. WYNE: So then, do a clinical trial that shows if you take this device or diagnostic A1c device into a CLIA-waived setting, and in that trial, show that you diagnose the diabetes sooner and that the people seek care, receive care, and prevent complications sooner, because I would argue that we don't have that data. So we don't have any proof that putting this into a CLIA-waived setting is going to make any difference to clinical outcomes. If we had that data, which is, again, beyond the technical issue, then it absolutely becomes valuable to put it into that setting. And ADA is arguing that we don't.

DR. WATSON: Doctor --

MS. McCOLLISTER-SLIPP: We do have a lot of data to suggest that people aren't hitting their targets, and that's within their traditional healthcare --

DR. WATSON: Yeah.

UNIDENTIFIED SPEAKER: That's not what this is about.

MS. McCOLLISTER-SLIPP: No, I know that's not what this is about, but --

DR. WATSON: Okay. Dr. Rej?

DR. REJ: Okay. This is to follow up on what Dr. Nipper mentioned earlier. In addition to all the PT requirements, I think one of the concerns about the testing done in certificate of waiver facilities is the control of storage of reagents, the quality control measures that are in place. And they may not be as rigorous. I'm not saying that they are, but they may not be as rigorous as those in either moderately or highly complex laboratories. And I would want to be sure that the manufacturer has really locked down that -- well, certainly, expired reagents is easy, but reagents that have not been stored and will not perform adequately will be prevented from producing results. That data hasn't been presented. The FDA I'm sure will ask for it, but I think that's something that the manufacturer would need to do, because, again, I think it's the -- these facilities may not have adequate control for refrigeration and so on, particularly if they're somewhat mobile.

DR. WATSON: Thank you.

Yes?

MR. THURAMALLA: Just to clarify on that point to Dr. Rej, I think the Sponsor's presentation included, among the safety features, conditions such as storage, and if they were not stored in a particular or prescribed range, that the device would actually shut down.

DR. REJ: Yes. But this was done by a camera looking at volume, and I'm not certain

that's adequate.

DR. WATSON: There was a -- oh, there.

DR. McSHANE: I'd like to just go back to these success rates and the proficiency testing. So can someone tell me what the sample size was? How many tests are they sent for which they have to get either two-thirds correct or 100% correct? Is the two-thirds, do you have to get two of the three challenges correct?

DR. WATSON: Yes.

DR. McSHANE: Okay. And how about the 100%? How many -- you also sent three tests, three samples, or --

DR. SCOTT: Two.

DR. McSHANE: Two? Okay. I mean, as a statistician, those are both absurd. I mean, you could only tell the difference between someone who completely does not know what they're doing and someone who has reasonable chance of knowing what they're doing. So I would go back to Dr. Rej's comment that, in a way, this whole proficiency testing thing is almost -- I shouldn't use the term -- but a surrogate marker for the general quality of, you know, the testing setting and I think also, in this situation, the clinical context in which the test results are going to be, you know, taken in and interpreted. So I don't think we should get too hung up on positive and negatives. There are lots of places where we have, you know, individual assessments that are actually not effective at all, but it's the bigger picture and the fact that they will correlate with the general quality of the healthcare setting, be it where the testing is happening or where the clinical decisions are being made.

DR. WATSON: Excellent points. Thank you.

Okay. Alan?

DR. REMALEY: I don't think it's an issue here, but the other issue about proficiency

testing is that the materials aren't necessarily commutable. So you're not really necessarily testing accuracy, although I don't think that's the issue in this case. You're really seeing whether -- you're testing precision of whether they're operating per the manufacturer. So if we want to kind of open this outside this discussion, I think all PT testing is not the same. So its relative importance differs depending on the quality of the PT testing --

DR. WATSON: Exactly.

Okay. Yes?

DR. WYNE: You know, if I make the wrong diagnosis one-third of the time, I don't think I'm considered to be a very good physician.

DR. WATSON: So I'm --

DR. NIPPER: This is Nipper. The two things are not analogous in any way.

DR. WATSON: So the question we're asked, Question (b): Is there any risk to health associated with the use of this device in CLIA-waived point-of-care settings? Are there potential mitigations that might be employed? We didn't talk about mitigations at all. Any thoughts?

DR. LIAS: I did hear one mitigation for flex studies for stabilities of reagents. That type of thing is helpful.

DR. WATSON: Sorry. Thank you, thank you.

Any other mitigations?

DR. BURR: One that crossed my mind, just to kind of get away from this ADA bugaboo, is that if the result were presented with a confidence interval, that might help people who are looking at it understand better what the result means rather than a single number, just for what it's worth.

DR. LIAS: Do you mean an analytical confidence interval?

DR. BURR: I'm not sure where it could come from. It could certainly come out of the data from the machine performance, but I think it would be possible to determine, for example, with a high degree of confidence what the 95% confidence limits would be, incorporating all the aspects of the system, from performance of the instrument, collection of the sample, variance in the reagents. I think that would be a doable thing.

DR. LIAS: That can be done during the validation phase, but I think the ADA's concern doesn't have to do with the data they give us in our application. I think they have more concern about real-life use on the --

DR. BURR: Well, this would facilitate real-life use in that someone instead of being -- the result might be 6.5%, but the machine would say this is somewhere between 6.3 and 6.7; do with it what you want.

DR. LIAS: We typically would get confidence intervals during the clearance phase and also in the waiver phase to make sure that the lower bound is acceptable.

DR. BURR: Yeah. I mean, this is all driven by this ADA 6.5% magic, so --

DR. WATSON: Dr. Henderson?

DR. HENDERSON: Yeah, I agree with you. I agree with you. That was the point I was asking him about, if we gave a range and didn't say this was diagnostic, but it was in here, and maybe it was a screen, use it more of a screening, and he said no.

DR. WATSON: Can I take another Chair's prerogative? Can I poll the Panel? If the ADA continues to say point-of-care testing without proficiency testing is not recommended, is there any amount of data that would convince us otherwise? I mean, I'm asking just for -- just a straw poll. Is it that's going to be a deal-breaker for you? Yes. Or the ADA notwithstanding, you could still see a way to say that this is probably -- I could get enough data that would allow me to say CLIA-waived point-of-care testing is okay?

DR. HENDERSON: First?

DR. WATSON: Yes, you first, yes.

DR. HENDERSON: Yes.

DR. WATSON: So you say, yes, there are --

DR. HENDERSON: Yes. I think that it is acceptable, I think, yes.

DR. WATSON: Even if the ADA continued to say no, you would -- you could say yes?

DR. HENDERSON: Even if the ADA continues, yes.

DR. WATSON: Dr. Nipper?

DR. NIPPER: No.

DR. McSHANE: I guess I'd have to say no.

DR. WYNE: Okay. So I'm not clear what a yes or no would be, but I am in line with the ADA, so that even if it showed me technically in the CLIA-waived setting it maintains the current performance level, that is not telling me that it can be used --

DR. WATSON: So your answer is no.

DR. WYNE: Okay.

DR. WATSON: Your answer is no.

DR. WYNE: Okay. Just want to make sure.

DR. WATSON: Dr. Burr?

DR. BURR: No, I would not pay attention to the ADA.

DR. WATSON: So your answer is yes.

DR. BURR: Yes.

DR. WATSON: Dr. Kwong?

DR. KWONG: Sorry. I'm a little confused.

(Laughter.)

DR. WATSON: I know. It was a clumsy way of stating -- but I think I'm getting the feel that it's about half and half.

So the question was if the ADA continues to say that point-of-care testing is not recommended, would you ever deviate from that? There are some data that some people say, yeah, if you gave me the right data, I would say yes. There are other people that say, no, I'd still say no if the ADA says no.

DR. NIPPER: Dr. Watson, in your original question, you pointed out the proficiency testing.

DR. WATSON: Exactly.

DR. NIPPER: So that was --

DR. WATSON: That was just what the ADA's major --

DR. KWONG: If it's the deal-breaker, as far as the ADA is concerned, is what it is, proficiency testing or not, then would say no.

DR. WATSON: No?

Alan?

DR. REMALEY: I don't think, Dr. Watson, that's a useful question because I think the FDA is an independent body. And I share some of the same concerns, but if I understand -- maybe I'm -- we're all interpreting --

DR. WATSON: Well, that's their -- that was --

DR. REMALEY: Maybe we're all interpreting this question differently, but I say no, I would like to line up with the ADA, but the FDA is an independent body, and I think we have an independent decision to make, although I share some of the concerns about having an accurate test.

DR. LIAS: I'm not sure if that no was the same as the other noes.

DR. WATSON: I know. I think that no was actually really a yes.

DR. REMALEY: Okay.

DR. REJ: Okay. I think I vote no, and a real no, and part of that is because the ADA

said that their standards are evolving, and I think that if there is sufficient data that shows that in this environment there's no risk for misdiagnosis or very minimal risk for diagnosis, and the ADA accepts it, then I think that that would be okay.

DR. WATSON: Okay.

MS. McCOLLISTER-SLIPP: And I have no idea if I'm answering yes or no or really what the question is, but I mean, I think it's perfectly acceptable, if not expected, for ADA to have a different perspective than FDA because they're two different groups for completely two different settings. And as Bob said earlier, their standards evolve.

DR. WATSON: Yeah.

MS. McCOLLISTER-SLIPP: They meet every year, and they consider new evidence. And they have not -- based on my understanding --

DR. WATSON: So your answer is yes.

MS. McCOLLISTER-SLIPP: They have not reviewed the data that we saw today.

UNIDENTIFIED SPEAKER: No.

DR. NIPPER: I hear a no.

MS. McCOLLISTER-SLIPP: I don't know what I'm answering. I don't know --

DR. WATSON: Okay. So the ADA is not a deal-breaker. So even if they said never use it, if you saw data that convinced you otherwise, you could say yes?

MS. McCOLLISTER-SLIPP: Yes, I think.

DR. WATSON: So you are a yes.

MS. McCOLLISTER-SLIPP: Well, I mean, I think it's okay that they say --

DR. WATSON: I wish I had never asked this question. I'm sorry I did.

(Laughter.)

MS. McCOLLISTER-SLIPP: I mean, it's okay that the FDA decides something that is currently not consistent with ADA recommendations.

DR. WATSON: Yes. So that's a yes. That's a yes.

MS. McCOLLISTER-SLIPP: Okay. If that's a yes, then --

DR. NIPPER: With great respect, Madam Chair, I think you're changing the question as you go around the room, and I --

DR. WATSON: I apologize.

(Laughter.)

DR. WATSON: So I really only wanted a sense of the people who felt like this is what the ADA says, we're not going to go against it, and that's obviously not what the FDA asked us to do, but there are certain --

DR. NIPPER: Well, you heard Dr. Rej say the ADA is open to change --

DR. WATSON: Right.

DR. NIPPER: And they say they don't have the data.

DR. WATSON: Right.

DR. NIPPER: And so I'm willing to listen to the ADA and watch them change.

DR. WATSON: Right. That's what --

DR. NIPPER: Okay. Would that -- but that's a no.

DR. WATSON: That's what we recorded you as.

DR. NIPPER: Yeah. But I think she said a no also.

DR. WATSON: No, she said a yes.

(Laughter.)

MS. McCOLLISTER-SLIPP: (Off microphone) question I would answer.

DR. WATSON: Okay. I am so sorry I opened that up.

DR. NIPPER: We got --

DR. WATSON: I'm sorry. If you don't want to answer, I totally understand.

MS. DAIGLE: I think I would answer yes.

MR. THURAMALLA: So I would answer yes, but I'm an Industry Representative. And therefore, the reason I'm answering yes, and the reason I'm spending one moment on this -- so this device, even without the Dx system, is already in the labs, is already in use, so it is already -- there's a higher chance/possibility it's being used for diagnosis.

DR. WATSON: We know it is.

MR. THURAMALLA: So, therefore, this question is automatically a yes as an Industry Representative.

DR. WATSON: Great. Okay. I appreciate everybody can disagree, but it's probably helpful for you to know how much disparate opinion there is.

DR. LIAS: No, it's definitely helpful. I mean, I do want to clarify. There's no sense from us that we think we cannot make a decision different than the ADA's recommendation.

DR. WATSON: Oh, exactly.

DR. LIAS: Our actual goal was to have the discussion in public to understand some input from the clinical community on this issue so that if we did decide to go a different way than the ADA's recommendation, then at least we understood whether or not, you know, that made sense or that type of thing. So it's not -- there's no sense from FDA that we must do what clinical guidelines say, but we seriously consider them, and that's what we're doing today.

MS. McCOLLISTER-SLIPP: I just have to say as a patient, I feel like the FDA's bias, you know, barring some sort of risk for communicable disease or something horrible, I think FDA's bias should be in favor of new technology, especially if there's good evidence to suggest that it's accurate. And based on what I saw, it looks like I would rather have this than some of the laboratory tests that I've probably had over the years, so --

DR. WYNE: You know what? I mean, what you're raising as the whole issue is none

of us are arguing against the technology. Those of us who, I guess, voted no, we're saying we share the ADA's concerns of how the technology is going to be used and applied. And that's what's not clear. And if data shows us that it's going to be used in a way that's positive, that it's going to -- if it can facilitate not just diagnosis but action on that -- you know, where is the data? What I found interesting was Dr. Kahn says there's no data that there's increased psychological distress if you get this number, and I was shocked by that. And I've already made a note to check with Dr. Polonsky and find out if that's really true because it seems to me that there is data. I know my IRB thinks there's data that you cause serious distress by doing this test on people. But the issue isn't the technology. The issue was how is it coming into medical use, the medical community, the lay community, and how is it all integrated together? That's the concern of the CLIA waiver on the part of the American Diabetes Association.

DR. HENDERSON: But I would argue that it's not -- it is minimally stressful because it is not a diagnostic tool outside of the health setting. It is something to bring you into the health center and to give you some information. As you said, you know your family history. You know you're already at risk. So that's stressful enough. And I don't believe that this being used outside of a health setting is diagnosis. It doesn't give you that diagnosis.

DR. WATSON: Well, their application is for a diagnosis.

DR. HENDERSON: Well, but if it's used outside of the healthcare setting -- I mean, that's what they're arguing in ADA is that the concern is that when it's used outside of the healthcare setting and patients don't have that interaction or individuals don't have access to getting information about what to do with it or what it means, then that's a problem. But I think if for some reason it gets, you know, put into the, you know, the church basement to do a screening, essentially, and then they say you have diabetes because of

this diagnosis, it does not make diagnosis. If you give somebody a number in the basement of a church, that's not a diagnosis. And even if the machine says it is, they don't have a diagnosis until they go to a healthcare provider or somebody that actually looks at them and talks to them and makes a diagnosis.

DR. WYNE: But if it's approved as a CLIA-waived test, it can go into the church basement and be used for the diagnosis.

DR. HENDERSON: But it won't be in their healthcare record. That doesn't give -- that doesn't make them have diabetes --

They're not then labeled. They're not official labeled as having diabetes because nobody has seen them to confirm that that's a diagnosis. It gets them into the healthcare center. It gives them information to go use it, but that's not the fear of getting insurance and jobs and that having implications, because there's nothing official about that. That just gets you to motivate you to go see somebody.

DR. WYNE: But it doesn't. That's part of the problem. It doesn't.

DR. WATSON: And we can't really --

DR. HENDERSON: But you're no worse off, though. You're no --

DR. WATSON: We can't debate this, so --

DR. HENDERSON: I mean, that's not going to damage -- you're no worse off.

DR. WATSON: Yeah, we can't debate this here. We'll continue --

DR. BURR: Just a quick question.

DR. WATSON: Yes?

DR. BURR: What about blood pressure cuffs in the grocery store?

DR. WATSON: What is your question?

DR. LIAS: They aren't covered by CLIA.

DR. BURR: What?

DR. LIAS: They're not covered --

DR. BURR: No, no, but in terms of -- it's the same principle. It's exactly the same principle, so --

DR. WATSON: Well, but the principle is the maker of that blood pressure cuff did not come to you asking for a diagnostic claim, so --

DR. BURR: Which means they're significantly less reliable.

DR. WATSON: Okay. I apologize that I don't think I gave you the answer you needed, did I?

DR. LIAS: I think we got a lot of good information. You know, I think what we're trying to understand is, you know, when an application like this comes in, are there things that we should be assessing that aren't typically assessed for a CLIA waiver? You know, we do ask for data in the hands of untrained users. They will have to look at that data with respect to the decision points for diagnosis. They will have to stress the system and try to understand what might cause the system to fail. But with respect to the ADA concerns, we were asking whether there are other things that we should ask them to cover if they were to come in. So if people have those suggestions, that would be helpful. If they don't, I understand.

MS. McCOLLISTER-SLIPP: I just have to say that as a patient who has lots of things that I have to measure, it really drives me crazy that there's been so little innovation in home-use monitoring. So, again, I mean, especially for hemoglobin levels, because I have anemia and I have like 18 other things that can make me tired, so figuring out exactly what that is is really frustrating, and the fact that I have to go get a doctor's orders, go to a lab, get all that done. I think the bias of FDA, which is completely separate than what ADA is because they're doing clinical practice recommendations, I think the bias of FDA should be towards letting new innovation get to the market and be there because that's better for

everybody. We don't know what's going to happen as this stuff proliferates. There may be uses that are wonderful that we can't anticipate. And I think the relative risk versus the possible benefit, in that equation, the benefit turns out to be much stronger. I think ADA's recommendations make absolutely perfect sense for ADA, but that's different than what you guys are charged with, so --

DR. WATSON: Dr. Remaley?

DR. REMALEY: Courtney, I don't recall the details, but what I recall from the slide is that you had 9 users, 360 samples, over a course of 2 weeks? Is that the kind of study --

DR. LIAS: That's a minimum. There's multiple sites and some other things.

DR. REMALEY: And do you have some latitude in terms of the criteria that one has to fulfill to get a CLIA waiver?

DR. LIAS: The guidance doesn't mandate criteria for particular tests. It's based on sort of the clinical situation of use. So we would try to develop what's called an allowable total error for the particular type of test.

DR. REMALEY: Right. Because as you probably know, the problem with the lack of oversight and the lack of PT is that you can buy an analyzer, you can have a great person to operate it, but over time, it deteriorates, and the lack of ongoing follow-up and whether you can build into criteria some sort of continued measurement or a greater span of time -- but I think that's -- I was a little bit alarmed when I saw that slide because I thought, you know, they may achieve that, and then in 2 months, the next lot falls apart. And I think that's the big concern about not having ongoing professional and proficiency tests, because you won't be aware of --

DR. LIAS: Do you have something in mind?

DR. REMALEY: Not specifically, but I see that's a hole in the criteria that one has to fulfill.

DR. LIAS: So are you talking about sort of more the stability of the instrument performance or --

DR. REMALEY: Yes.

DR. LIAS: -- are you talking about lot-to-lot performance?

DR. REMALEY: Both.

MS. McCOLLISTER-SLIPP: And that, to me, looks like a great opportunity for postmarket studying or surveillance, you know, whether it's, you know, real-world data, but I don't think that that should be a barrier to approval.

DR. WATSON: Yes, Dr. Wyne?

DR. WYNE: Okay. So you asked what ideas do we have, and just I'm trying to think about technology and things that happen. And the first thing that came to my mind is, you know, my patients can go and get a mammogram without a prescription or a physician's order, but they have to have a name of a physician that the result can be sent to. And with the kind of technology we have nowadays, how hard is it to create some kind of app that in that setting, the person is entered in and their primary care clinic information is entered also so that the result is automatically electronically sent to them. And as the electronic medical records are supposed to become more sophisticated and able to talk to each other, there should be away to automatically send it to the physician a person designates.

I know it's not perfect. Sometimes mammogram reports come to me as an endocrinologist, and I don't know what to do with them. But the point is that there could be, whether it's an app or something, that it can even be built into that device that you're entering the person's name and date of birth and their primary care clinic. And I know that with the electronic systems we have now -- like if I want to send a letter to a physician, many physicians across the country are built into our EHR, and I just type in

their name and I find them, and not necessarily in my local area. I find people in other states that I can send letters to.

So I'm just envisioning using the electronic tools we have and things that are in development, that there could be a way that that report from that CLIA-waived setting does actually get to someone who potentially could contact the patient and act on the results.

DR. LIAS: Yeah. So thank you for that suggestion.

DR. WYNE: I mean, it's kind of --

DR. LIAS: We'll certainly think about it. I do want to remind everyone, though, this is a prescription device, and it can't be ordered without an authorized prescribing --

DR. WYNE: So even when it's CLIA waived?

DR. LIAS: Right.

DR. WYNE: So then who's responsible for the prescription when they're doing it in a screening setting?

DR. LIAS: Somebody will be there who has prescribing authority.

DR. WYNE: And so that person is legally responsible for those results?

DR. WATSON: Dr. McShane, do you have a comment?

DR. McSHANE: I was just going to raise the issue of there are plenty of people who do not have a primary care physician, but I think you just answered that question. So if you did it in a church basement, there's going to be some M.D. who's willing to accept all these reports that would be sent to your model --

DR. WYNE: With its attendant liability --

DR. BURR: Oh, that's not the way that happens. Screening doesn't work that way. They do the church basement, somebody borrows one from the corner clinic, and maybe an RN is there to operate it, maybe not.

DR. LIAS: The states differ in who is authorized to prescribe products.

DR. WATSON: All right. So have we answered 3b?

(Pause.)

DR. LIAS: I think that's very helpful. Thank you.

DR. WATSON: Thank you. Okay. And I do want to say if we have additional thoughts or information, we can e-mail or send them to you somehow?

DR. LIAS: They wouldn't be part of these official Panel discussions, but certainly anyone in the public or on the Panel can always contact us for good discussions.

DR. WATSON: Okay. Thank you very much.

Does anyone have any thoughts or comments that haven't -- you think we haven't covered?

(No response.)

DR. WATSON: Anything from your point of view that we haven't covered?

DR. LIAS: No. I just really want to thank everyone for their time today. I want to emphasize that we work with a lot of clinical associations, and practice guidelines are a large part of how we consider clinical validity and safety and effectiveness and substantial equivalence. And we use the clinical guidelines to help us understand how tests are used and help us to try to understand the issues that we may need to consider or not, depending on what's being put in front of us. So today was extremely helpful for us to have sort of a public discussion of what the issues were with respect to some decisions that we may have to make in considering how we should look at clinical practice guidelines that are in place. And so I really want to thank everyone for their input on that.

DR. WATSON: And I want to thank the excellent Panel, as well. This has been really, really useful. And I think we gave the FDA the flavor that these are complex decisions, and there's not one answer.

Well, thank you very much. With that, I will call this meeting adjourned.

(Whereupon, at 2:34 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL

July 22, 2016

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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PATRICK SERIO

Official Reporter