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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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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March 30, 2018
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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MARC S. RENDELL, M.D.	Voting Member
KATHLEEN WYNE, M.D.	Voting Member
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MICHAEL AVILES, HSCM, USCG	Temporary Non-Voting Member
SHERRY KIRKPATRICK, B.S.N., RN	Temporary Voting Member
ROBERT REJ, Ph.D.	Temporary Voting Member
HENRY C. NIPPER, Ph.D.	Temporary Voting Member
JOHN R. ASTLES, Ph.D.	Temporary Voting Member
HUGH A. CASSIERE, M.D., FCCP, FACP	Temporary Voting Member
ROSEMARY KOEHL LEE, D.N.P., RN	Temporary Voting Member
GABRIELLA LAKOS, M.D.	Industry Representative
CAROLYN PETERSEN, M.S., M.B.I.	Consumer Representative
ANNA McCOLLISTER-SLIPP	Patient Representative
PATRICIO G. GARCIA, M.P.H., CDR, USPHS	Designated Federal Officer

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M E E T I N G

(8:03 a.m.)

DR. BREMER: So I'd like the call the meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee to order.

I'm Andrew Bremer, and I have the pleasure and privilege of being the Chair of this panel. My background is in training in pediatrics internal medicine and pediatric endocrinology, with a focus on diabetes technology and closed loop platforms.

I note for the record that the members present constitute a quorum as required by Title 21 of C.F.R. Part 14. I also would just say I'm at the National Institutes of Health. Sorry about that. I would also like to add that the Panel participating in the meeting today have received training in FDA device law and regulations.

For today's agenda, the Committee will discuss, make recommendations regarding the general use of blood glucose meters with capillary samples from patients throughout the hospital environment and is not related to a particular premarket submission.

It is worth noting that portable blood glucose meters that measure blood glucose values are used by millions of people every day as an aid in diabetes self-management. These types of devices are also used by healthcare professionals in a variety of clinical settings, including acute and chronic care facilities, general hospital wards and intensive care units, physicians' offices, emergency departments, assisted living facilities, and nursing homes.

Before we begin, I would like to ask our other distinguished Panel members and FDA staff seated at the table to introduce themselves. Just for the record and for those in the audience, I'll ask that you state your name, your area of expertise, your position, and affiliation, and I'll start with Dr. Lias.

DR. LIAS: Good morning. My name is Courtney Lias. I am the Director of the

Division of Chemistry and Toxicology Devices at FDA, and we're the division that regulates glucose meters. Thank you.

DR. CASSIERE: Good morning, everyone. Hugh Cassiere. Specialty is critical care. I'm the Medical Director of Cardiothoracic Intensive Care Unit in North Shore University Hospital, and I'm the Chief of Critical Care for the Department of Cardiovascular and Thoracic Surgery at the hospital.

DR. ASTLES: Good morning. I'm John Astles. I work at the Centers for Disease Control. I'm a board certified clinical chemist and have been at the CDC for about 20-some odd years and provide support to CMS on CLIA issues.

DR. LEE: Hello. I am Rosemary Koehl Lee. I'm a clinical nurse specialist. I have my doctorate in nursing practice, and I'm the clinical nurse specialist for the critical care and progressive care units at Homestead Hospital in Homestead, Florida.

HSCM AVILES: Good morning. My name is Michael Aviles. I'm the Health Services Rating Force Master Chief advisor to the Chief Medical Officer to the Coast Guard. I'm also the oversight for medical programs in the Coast Guard, such as emergency medicine and the corpsman rating in the United States Coast Guard, and I'm stationed out of headquarters, Washington, D.C.

DR. TUNG: Good morning. I am Avery Tung. I am a critical care anesthesiologist at the University of Chicago.

DR. GRUNBERGER: Good morning, everyone. I'm George Grunberger. I am an adult endocrinologist and diabetologist, doing diabetes now for 38 years. I'm also a Past President of the American Association of Clinical Endocrinologists.

CDR GARCIA: Good morning. My name is Commander Patricio Garcia. I'm a Health Services officer, and I'm the Designated Federal Officer for this meeting. I am currently assigned to the Food and Drug Administration in the Office of Community Management.

DR. RENDELL: Marc Rendell. I'm Medical Director of the Rose Salter Medical Research Foundation. I specialize, again, in diabetes and endocrinology.

DR. WYNE: I'm Kittie Wyne. I'm an adult endocrinologist specializing in diabetes at the Ohio State University.

DR. NIPPER: Good morning. I'm Henry Nipper. I'm Professor of Pathology at Creighton University in Omaha, and I've had responsibilities for toxicology and clinical chemistry.

DR. REJ: Good morning, everyone. I'm Robert Rej. I'm Director of Clinical Chemistry and Hematology at the New York State Department of Health, Wadsworth Center, and Associate Professor of Biomedical Sciences at the School of Public Health, State University of New York at Albany.

MS. KIRKPATRICK: Good morning. I'm Sherry Kirkpatrick. I'm an emergency room nurse with a focus on diabetes education, from Lake Geneva, Wisconsin, Mercyhealth.

DR. LAKOS: Good morning. I am Gabriella Lakos. I am a clinical pathologist, currently Medical Director for Abbott Laboratories, Hematology Division. I am the Industry Representative on this Panel.

MS. PETERSEN: Good morning. I am Carolyn Petersen. My background is exercise physiology and medical informatics. In my day job, I am Senior Editor of mayoclinic.org. I am here on this panel as Consumer Representative. The views expressed are my personal views and do not reflect the policy or position of Mayo Clinic.

MS. McCOLLISTER-SLIPP: And I'm Anna McCollister-Slipp. I am here as a Patient Representative, but my background, professionally I do health data analytics, and I'm working on creating a platform for crowdsourcing the design of research and other researchy kinds of things.

DR. BREMER: Great. I want to thank everyone on the Panel for taking time out of

your day jobs to be here and to be a part of this discussion.

For those in the audience, if you have not already done so, please, either now or at a break, do sign in on the attendance sheets that are out by the doors. Again, we want to capture everyone's participation and presence here at the meeting today.

Commander Patricio Garcia, to my left, of the United States Public Health Service, as he mentioned, is the Designated Federal Officer for this meeting today, and I will now let him make some introductory remarks.

Commander.

CDR GARCIA: Thank you, Chair. Good morning, everyone. I will now read the Conflict of Interest statement.

The Food and Drug Administration (FDA) 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 the Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Subparagraph 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.C. Subparagraph 208, Congress has authorized FDA to grant waivers to special Government employees or 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 purposes of 18 U.S.C. Subparagraph 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 regarding measuring blood glucose capillary blood with blood glucose meters in all possible patients, including those receiving intensive medical intervention or therapy and patients with decreased peripheral blood flow, such as with severe hypotension, shock, similar hyperglycemia, and severe dehydration.

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.C. Subparagraph 208.

Dr. Gabriella Lakos is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Abbott Laboratories.

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 firms 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.

Before I turn this meeting back over to the Chair, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Tara Rabin.

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 are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with AnnMarie Williams, who is at the registration desk right now.

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

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

Thank you very much.

Dr. Bremer.

DR. BREMER: Thank you, Commander Garcia.

At this time, I would like to welcome Dr. Courtney Lias, Division Director of the Clinical Chemistry and Clinical Toxicology Devices in the Center for Devices and Radiological Health. Dr. Lias will make opening remarks.

Next will be Dr. Leslie Landree. The diabetes team lead in the Clinical Chemistry and Clinical Toxicology Devices Branch will present an overview of clinical studies done using blood glucose monitoring systems in hospital settings utilizing capillary blood samples.

Dr. Lias.

DR. LIAS: Thank you.

Hello. My name is Courtney Lias. I am the Director of the Division of Chemistry and Toxicology Devices here at FDA. Thank you for agreeing to sit on our Advisory Panel today and provide input on this important topic.

I will provide a brief introduction of why we have convened the Panel today. There's been much public discussion over the last decade regarding the use of blood glucose monitoring systems, often abbreviated BGMS, in hospital settings. These devices have become critical tools for patient management. They are small and portable, easy to use, at the patient's bedside, require more affordable reagents than similar bedside glucose tests, and generate a result quickly with only a small amount of blood.

Modern era glucose meters were originally designed as home-use devices. Clinicians recognized the value of near-patient glucose testing, and these home-use devices migrated into healthcare settings. This included physician offices as well as in-patient facilities.

In the last 10 years, there has been much discussion within the glucose meter community among laboratory scientists, endocrinologists, researchers, glucose meter manufacturers, and government agencies about BGMS accuracy requirements for different uses. Patient populations across the hospital vary, and the reasons for blood glucose monitoring vary across patients as well. For example, some patients are tested for routine glucose monitoring while others are tested to inform acute decisions, such as insulin dosing. These different uses carry different risks.

One example of the variable uses of glucose testing in hospital is the use of glycemic control protocols in the ICU. Glycemic control protocols became more common in the early 2000s when clinical data out of Greet Van den Berghe's lab in Leuven, Belgium, demonstrated that reducing hyperglycemia in intensive care patients led to better clinical outcomes. Her group demonstrated lower mortality in intensive care patients when

glucose levels were managed to a strict range of 80 to 110 mg/dL, using infused insulin by expert nursing staff. This practice of managing blood glucose was known as tight glycemic control. Glycemic control protocols were implemented globally, though the protocols used varied across hospitals.

Additional clinical trials were launched to study outcomes related to tight glycemic control, but they were not all able to replicate the results from Leuven. For example, the NICE-SUGAR study was discontinued after an increase in mortality due to hypoglycemia was observed in the tight glycemic control arm.

There has been a lot of discussion about why NICE-SUGAR may have failed to show a benefit of tight glycemic control since there was a broad consensus that limiting hyperglycemia is good for patient outcomes. Several potential reasons for the different outcomes include varying levels of insulin dosing expertise in the study staff, different target ranges for blood glucose used, different nutritional strategies, and different types of insulin administration.

In addition, many pointed to the use of different specimen types, for example, venous or arterial versus capillary blood, and the different instruments used to measure blood glucose across sites as contributing to inaccurate dosing in these ICU patients. While the nurses in Leuven used blood gas analyzers to measure glucose in venous and arterial blood, institutions in the NICE-SUGAR study varied in blood glucose measurement methodology, and many sites used capillary blood measured by BGMS.

Following these results, many institutions continued to implement glycemic control protocols in intensive care units but no longer targeted tight control due to fears of hypoglycemia. Many glycemic protocols in use today are more conservative and aim to keep patients at approximately 150 or 180 mg/dL.

These study results prompted increased discussions of the accuracy requirements for

hospital use glucose meters, and the clinical, regulatory, and manufacturing communities began developing standards for hospital-use glucose meters. In January 2013, the Clinical and Laboratory Standards Institute, abbreviated CLSI, published POCT12-A3. This guideline contains information to assist hospitals in verifying and validating glucose meters for use in hospital settings and recommends performance goals for glucose meter accuracy throughout the hospital setting. This document also recommends that in assessing glucose meter performance, hospitals consider special subpopulations, including patients in glycemic programs in intensive care units.

The expert committee that developed this document recommended that glucose meters used in hospitals be within 12½% if greater than 100 mg/dL, or within 12 mg/dL if below 100 mg/dL, of a laboratory method 95% of the time. They also included recommendations limiting the number of outliers.

In addition, in 2010 FDA held a public meeting entitled Clinical Accuracy Requirements for Point of Care Blood Glucose Meters. The purpose of the public meeting was to discuss clinical accuracy requirements in blood glucose meters and other topics related to their use in healthcare settings. The workshop included a session entitled Tight Glycemic Control in Clinical Settings, which included presentations and discussions from physicians, laboratories, government, industry representatives, and patient advocates.

Following discussions at this public meeting, FDA published a draft guidance that proposed the types of studies manufacturers of glucose meters intended for use in healthcare settings should perform to assess performance and included proposed performance goals for accuracy. Based on hundreds of comments received on the draft guidance document, FDA published a final guidance in October of 2016, which included revised accuracy performance goals for these devices.

The community recognizes that glucose meters may have different performance in

different specimen types and different patient populations. Across different types of healthcare settings, there is also a wide range of expertise in glucose meter users. In this guidance, FDA recommends that manufacturers specify the healthcare settings they intend the glucose meter to be used in and validate meter performance in those settings and patients. Therefore, if a manufacturer wants to claim that a glucose meter can be used in hospitalized patients all over the hospital, they would perform a validation study in all hospital patient populations and with each claimed specimen type.

As I mentioned, the glucose meters used in hospitals were originally designed and validated for home use. Even when intended for hospital use, manufacturers have generally performed accuracy studies more suited to a home-use population rather than a sicker hospitalized population. Accuracy studies were performed in a relatively healthy ambulatory population, even though the devices were used in a wide variety of patient populations. These devices were also labeled with limitations against use in certain populations, including patients receiving intensive medical care.

The Center for Medicare and Medicaid Services, or CMS, regulate laboratory testing under CLIA. Because glucose meters were designed and cleared as home-use devices, they were considered waived under CLIA. However, CMS stated that if a facility uses a glucose meter off label, including in patients, like ICU patients that are limited by the meter labeling, the glucose meter should be considered a high-complexity test. If a facility uses a glucose meter as a waived device in patients in intensive care, the device must be labeled for that claim or the laboratory may risk losing accreditation under CLIA.

Dr. Landree will present additional information on waived versus high-complexity tests later in our presentation. However, I will summarize by saying that laboratories performing only waived tests are subject to minimal CLIA regulation. Laboratories performing high-complexity tests must comply with specific laboratory standards governing

additional aspects such as certification, personnel, and quality assurance. Only laboratories with certification for high-complexity testing may use a device off label.

In this case, the laboratory must perform larger analytical or clinical studies to demonstrate full test validation prior to offering the test for clinical use. The lab must also meet other applicable federal and state requirements for high-complexity testing, such as personnel training requirements. In many states, nurses would be prohibited from performing high-complexity tests at the bedside.

Hospital laboratories who had not considered glucose meter use in these setting as off label were troubled by the CMS clarification. The announcement caused considerable angst in the hospital community because these devices were routinely being used in all parts of the hospital as waived tests, including for patients receiving intensive care. Many healthcare facilities were unable to meet the high-complexity requirements and had to find less convenient alternative glucose tests in certain hospital wards.

To address this challenge that hospitals were facing, we at FDA encouraged manufacturers of hospital glucose meters to seek FDA clearance and CLIA waiver for use in all hospital populations, including for patients receiving intensive care. When a manufacturer does the validation to support clearance of a specific claim, it relieves the laboratory of the burden of full test validation and high-complexity requirements resulting from off-label use. In addition, the manufacturer can better support customers who use the device as labeled and can better take proactive steps to mitigate patient risks for these uses.

In 2014 Nova Biomedical became the first company to have a glucose meter with FDA clearance and CLIA waiver for venous, arterial, and neonatal heel-stick whole blood samples throughout all hospital settings. This clearance was supported by a large clinical study that compared venous and arterial glucose measurements using their meter to

laboratory blood glucose measurements in nearly 1,700 patients. However, the Nova Biomedical study did not include capillary blood specimens, and the limitations surrounding the use of capillary blood for testing in patients receiving intensive medical care remain in all hospital-use glucose meters.

We at FDA recognize the importance of having CLIA-waived glucose meters in all hospital departments. Additionally, we understand that being able to make capillary measurements in all hospitalized patients using FDA-cleared and CLIA-waived glucose meters would be more convenient and feasible for hospital staff.

So that brings us to why we're here today. We have recently become aware of three relatively large datasets assessing capillary blood in two different glucose meters in the intensive care setting. Dr. Landree will present these data to help the clinical community better understand the accuracy that can be expected from these devices in this setting. Our goal is to increase transparency surrounding how glucose meters are performing when used by nurses on patients receiving intensive medical care. We seek to obtain advice from our Advisory Panel on this topic and to hear public comment on this use of glucose meters.

Thank you. I'd like to introduce Dr. Leslie Landree, the diabetes team leader in our group, who will present the data that we have received.

DR. BREMER: Thank you.

DR. LANDREE: Thank you, Dr. Lias.

Hello, everyone. I'm Leslie Landree. I'm the diabetes team leader in the Division of Chemistry and Toxicology. Is that better? All right.

As mentioned in the previous talk, we have recently become aware of three relatively large capillary blood datasets in two different BGMS devices in the intensive care setting that may be helpful in understanding how these devices work in those populations and settings. Today I will be presenting the summary data from those studies.

But before we discuss the studies and review the data, I will briefly describe how we evaluate BGMS performance. Before blood glucose meters are marketed, we evaluate data provided by the manufacturer, submitted to support the intended use of the device. This includes information on how precise the device is across the measuring range. We also look at how different substances may affect performance, such as various medications or endogenous substances like uric acid or dopamine that may be present in the patient's blood and may affect meter performance.

Another part of our evaluation is the assessment of meter accuracy data. The type of accuracy information provided depends on the intended use of the meter. Blood glucose meters are used by very different and unique populations in a variety of settings. Most meters are used by healthy people with diabetes at home. In the home setting, these meters are usually used for self-testing, where people use the device to test their own blood glucose.

Glucose meters are also used in a variety of healthcare settings, including physicians' offices, hospitals, emergency departments, operating rooms, nursing homes, among other settings, where they are used for assisted testing rather than self-testing. Patients in these healthcare settings differ from home users in ways that may affect device performance. They may have conditions or may be taking medications that may affect meter accuracy. Therefore, when we assess accuracy, we look at how the meter works when it is being used by the intended user.

For a home-use meter, this is done by assessing the accuracy when the meter is used by lay user participants to test their own blood glucose.

For meters that will be used in healthcare settings, we look at how well the meter works when it's used by the intended operator, such as a nurse who is performing assisted testing on the patient. These studies take into consideration the disease states, patient

conditions, and medications that might affect device performance, and are conducted in an environment that is reflective of actual use settings in order to get an idea of how the meter will perform when it's used in that particular patient population and setting, such as the hospital or doctor's office or at home.

For these evaluations, the meter results are compared to a comparator method, which is an accurate and precise laboratory method. These studies include an evaluation of each of the different claimed sample types, such as venous or arterial or capillary blood.

One way to look at glucose meter accuracy is to present the number of results that are within a certain percentage of the laboratory comparator method. In the next several slides, we will be looking at accuracy summary data in this type of format, so we wanted to spend a little bit of time going over this type of presentation. In this example, accuracy results are presented in different bins, such as the percentage of meter results within 10% or 20% of the laboratory method.

Assessing accuracy data using only percentages is not always the best approach, since percentage changes at lower glucose concentrations are associated with very small absolute changes or mg/dL changes. Therefore, here and in the data in this talk, the results from glucose concentrations below 75 mg/dL are assessed as absolute mg/dL differences, that is, within 5, 10, 12, or 15 mg/dL, and all the results from glucose concentrations greater than 75 mg/dL are presented as percentages, 5%, 10%, 12%, 15%, 20% difference from the laboratory comparator method.

Seventy-five mg/dL glucose is used as the cut point here, but other cut points could be used. The cut point of 75 began to be used many years ago when the standard for glucose meter performance was +/- 20%. Fifteen mg/dL was 20% of 75, so the cut point naturally fell there.

Looking at the results from samples that contained glucose concentrations below

75 mg/dL separately from those greater than 75 has additional benefits as well. This allows the examination of results in the clinically important hypoglycemic range separately from the rest of the data. Higher cut points such as 100 mg/dL that is used in the POCT12 have benefits as well, but accuracy in the hypoglycemic range can be masked this way because there are generally more data points collected in the euglycemic range rather than the lower ranges.

As mentioned in the previous talk, Nova Biomedical received clearance in 2014 for the StatStrip Glucose Hospital Meter System for use in patients throughout all hospital and professional healthcare settings when used with venous whole blood, arterial whole blood, neonatal arterial and heel-stick samples. However, the study that Nova performed for this clearance did not include capillary blood specimens. Therefore, the labeling includes a limitation against the use of the meter with capillary samples in patients receiving intensive medical intervention and therapy, as do all other hospital glucose meters.

The study performed with this meter included samples obtained from almost 1,700 patients at five different hospitals, patients in areas throughout the hospital such as emergency rooms, operating rooms, and various intensive care settings such as medical, surgical, cardiovascular surgical, and pediatric intensive care units.

To provide some context for our discussions today regarding capillary sample data in hospitalized patients, the results from the Nova StatStrip study using arterial and venous blood samples used in the 510(k) clearance are summarized here. Here, the results from 1,468 arterial samples and 347 venous samples are summarized, with those results from samples with glucose concentrations less than 75 mg/dL presented in the top table separately from those with glucose concentrations greater than 75 in the bottom table.

Now, if we focus on the 12 mg/dL and 12% bins, which are similar to the bins used in POCT12, we see that the data for both arterial and venous samples are quite similar for the

samples with glucose less than and greater than 75, with approximately 96% to 90% of the meter values falling within 12 mg/dL or 12% of the laboratory comparator method for both types of samples.

Now, if we pull out the 12 mg/dL and 12% bins, we can see that the StatStrip has similar performance as compared to that recommended in POCT12. That states that 95% of the data should be within 12 mg/dL and 12.5%, though the cut points differ slightly in this comparison, with 75 mg/dL used in the StatStrip analysis and 100 mg/dL used in the POCT criteria.

In addition, these criteria also meet the performance goals described in FDA's guidance for BGMS devices, which similar to POCT12 recommends that 90% of the results fall within 12 mg/dL and 12% of the lab value but with 75 mg/dL used as the cut point.

As mentioned briefly a few slides ago, though the Nova Biomedical received clearance for hospitalized patients in arterial and venous blood, no information was provided on the performance of these meters with capillary samples from patients receiving intensive medical intervention and therapy. All hospital meters, including the Nova StatStrip meter, are labeled with limitations against the use of the devices in certain patient populations, including these patients receiving intensive medical intervention and therapy. Therefore, hospitals that use these meters with capillary samples in this patient population would be using the meters off label, and as previously discussed, this puts strain on the hospitals that use these devices.

To address this challenge, we have been working with manufacturers of hospital meters to encourage them to seek FDA clearance for use of these meters in hospital settings for all sample types, including capillary samples.

FDA has recently become aware of the three relatively large datasets in capillary blood for two different BGMS devices in the intensive care setting. We are unaware of

similarly large datasets for capillary blood in this patient population using modern BGMS technology. We have obtained permission from the sponsors of these studies to share this data in the context of this advisory panel meeting. Our goal is to raise transparency surrounding how BGMS devices are performing when used by nurses on patients receiving intensive medical intervention and therapy.

These data will help the clinical community better understand the accuracy that can be expected from these devices in this setting to improve patient care in the U.S. We seek to obtain advice from our Advisory Panel on this topic and to hear public comment on this issue of BGMS devices. In the next several slides, I will discuss each of these three studies and the results in more detail.

The three studies include two prospective studies and one large retrospective study. Two different blood glucose meters are used in these studies, and we are calling these meters, Meter A and Meter B. In each of these three studies, capillary test results obtained using the glucose meter were compared to matched measurements obtained using the laboratory comparator method.

The first study we will discuss is a study that was performed with the meter we are referring to as Meter A. In this study, 567 capillary whole blood finger stick samples were obtained from three different critical care units: cardiovascular intensive care, medical intensive care, and the operating room.

Capillary whole blood meter glucose results were compared to plasma results obtained on the central laboratory system, and though not the purpose of this study, meter results using arterial and venous samples from the same subjects were also collected and compared to the laboratory value. All BGMS testing was performed by the intended use operators within each of these three critical care settings, typically nursing staff.

Here are the Study 1 results for arterial and venous blood using Meter A. Because

the study sites had implemented glycemic control protocols, no glucose results below 75 mg/dL were collected, so there is only one summary table for this study with samples greater than 75 mg/dL. The results show that 98 percent of the results are within 15% of the laboratory values, and 95.5% are within 12%, and for these samples, there were no results greater than 20% of the lab value.

Using arterial and venous samples, the study generated similar data to that of the study used to support the clearance of the Nova StatStrip meter for arterial and venous blood samples. Here, you can see 95.5% within 12% from Study 1 compares to the 96% to 97% from the StatStrip within the same 12% bin. However, when capillary data from the same studies, same subjects in Study 1 were evaluated, the agreement with the laboratory value was different. Here, only 85.4% of the results were within 12% of the lab value and only 91% within 15%. In addition, you can see that there were values outside of 20%.

On this slide, you can better see the differences between the data collected in Study 1 when arterial and venous blood were used, with 95.5% of the results falling within 12% versus 85.4% when capillary blood was used in the same patient population with the same operators.

The next study we will summarize is Study 2. This is a large retrospective study of over 14,000 paired intensive care capillary samples using the same meter that was used in Study 1, Meter A. The capillary whole blood glucose results from the BGMS were compared to the laboratory plasma results. The samples used in the analysis were identified by meeting the following criteria: The enrolled patients were in critical care departments; a capillary result on the meter was obtained by the intended operator, which was typically a nurse; and plasma glucose results were obtained from the same subject on the laboratory method within 15 minutes.

In this large dataset, 85.2% of the capillary results were within 12 mg/dL for glucose

values less than 75, and 86% of the results were within 12% of the laboratory method for glucose values greater than 75. These results are almost identical to those from Study 1, where 85.4% of the results from the glucose values greater than 75 were within 12%, compared to 86% seen here in Study 2. In addition, there are a significant number of samples that exceeded 15 mg/dL or 20%.

Study 3 was performed using a different BGMS device, which we will refer to as Meter B. The study was conducted by collecting 345 capillary whole blood specimens from patients within critical care units. As with the previous studies, all BGMS testing was performed by intended operators within each of the critical care settings and, again, typically nursing staff. Capillary whole blood glucose results on the BGMS were compared to plasma results collected in parallel and measured on the laboratory method.

The capillary results of Study 3 are presented here and, again, are very similar to the results from Studies 1 and 2. For example, these studies demonstrate that with Meter B, 86.5 of the capillary results are within 12% of the comparator method for glucose values greater than 75, and 91.7% were within 12 mg/dL for concentrations less than 75.

Because Meter B is already available as an over-the-counter meter and has been evaluated in an ambulatory diabetic population, we can see that the capillary data in the intensively managed hospital patients is very different than the capillary data in this ambulatory population. In a healthier population, using Meter B for self-testing, 100% of the capillary results were within 12 mg/dL of the lab value for glucose concentrations less than 75, and 96.6 were within 12% for glucose values greater than 75.

Due to the similarities in the data between these three studies, we believe that they are likely representative of the data obtained when capillary blood measurements are made in this sick population using blood glucose meters. Here, we have presented the results of all three studies, along with the cleared StatStrip hospital meter data side by side. The

orange shaded rows are the new capillary data, and the green shaded rows are the cleared data for the venous and the arterial samples as well as the capillary blood samples in healthy population.

These results from glucose values less than 75 mg/dL show that the capillary results have fewer results within 12 mg/dL of the lab value than the venous or the arterial samples or the capillary samples obtained from the healthy population.

These results from the glucose values greater than 75 also show that the capillary results from hospitalized patients have fewer results within 12% of the lab value than the venous and the arterial samples or the capillary samples from the healthy population. There were also more values that exceeded 20% in this hospitalized capillary data.

We at FDA have been involved in many different types of discussions about glucose meter accuracy, including accuracy within hospitalized patients. Based on these discussions, it does not seem that the community is aware of the differences in meter performance demonstrated by these studies. There have been multiple opportunities over the past decade for discussion and comment on what the appropriate criteria should be for these meters in this patient population, but no criteria that has been proposed would allow for the capillary data we have just presented.

For example, there have been two recent external committees that have developed accuracy criteria for glucose meters. As discussed, the most relevant is POCT12, which makes recommendations on the performance hospitals should verify prior to using a meter on their patients. This standard was developed within a committee comprised of all stakeholders, including clinicians, laboratory scientists, members of industry, and government. This standard recommends that hospital glucose meters be accurate such that 95% of meter results be within 12.5% or 12 mg/dL of the laboratory value.

In the right-hand column, we've pulled the results from Study 2 that are the most in

line with the criteria in the middle column. Keep in mind, however, that the cut points are slightly different, with 100 mg/dL used in the POCT12 and 75 mg/dL used in Study 2. Even if analyzed with a cut point of 100 as proposed in POCT12, the data from the capillary studies presented would not meet the criteria of POCT12.

In 2016 FDA finalized a guidance document on BGMS devices that includes recommendations for performance goals for accuracy evaluations. The development of this guidance document included a draft document, public discussion and outreach, and comments from stakeholder community. We received hundreds of comments on this document, and many of these comments included proposals for different accuracy performance goals than were in the draft document. This table provides a summary of various accuracy goals from the FDA draft and final guidances as well as the most stringent and most permissive suggested criteria that were submitted as comments to the draft guidance.

When compared to these recommendations, the capillary data observed in these large studies, and summarized in the right-hand column, do not meet the performance goals in the finalized guidance or even the most permissive goals proposed by stakeholders in comments to the docket. We believe that this indicates that the stakeholder community, including glucose meter manufacturers, laboratory professionals, and clinicians, may not realize the differences in performance that can be observed in different sample types across different patient populations.

We cannot tell from these studies why the capillary data is so different from the venous and the arterial data. The study investigators have evaluated potential subpopulations within the study population, including looking at patient conditions, medications, and diagnosis; however, they have not been able to identify a discrete or definable population driving the lower accuracy performance with these BGMS devices and

capillary samples in hospitalized patients. We can speculate that possible factors could include compromised capillary blood flow in these patients, sample collection factors, or undefined patient conditions.

This data we have just presented demonstrates that glucose meters are clearly less accurate in intensive care settings when capillary blood is tested compared to when arterial and venous blood is tested. However, no device is perfect, and we do not mean to imply any judgment on whether the device is too inaccurate to be considered safe or effective for its intended use. We are presenting this data today to hear discussion from our Advisory Panel and the clinical community on this aspect of meter accuracy and clinical use.

During the Panel discussion sessions, we would like the Panel's feedback on the data observed and whether there are certain benefits and risks we should consider if asked to evaluate a device for this use.

The Clinical Laboratory Improvement Amendments, or CLIA, of 1988 was passed to ensure the quality of laboratory testing and therefore the quality of patient care. Any laboratory that performs testing on human specimens for the purpose of diagnosis, prevention, treatment of disease, or assessment of health must be certified under the CLIA regulations.

All in vitro diagnostic tests fall into one of three CLIA complexity categories: high complexity, moderate complexity, or waived. The type of CLIA certificate determines the complexity of the test that a lab is allowed to run. High-complexity tests require a high level of operator expertise and training and may require troubleshooting or several manual operator steps. For example, most mass spectrometry-based assays would be high complexity.

In addition, any test which is not CLIA categorized or is modified by the laboratory is by default a high-complexity test. In some states, the training requirements for operators

of high-complexity tests are relatively high, for example, medical technology degrees.

Moderate-complexity tests may include several steps, are usually automated, and require a moderate level of expertise from the laboratory personnel to run and maintain them. For example, many serum or plasma assays run on large automated analyzers that are categorized as moderate complexity.

Some tests are automatically waived, including urine pregnancy tests and visually read urine dipsticks. In addition, all tests intended for home use are waived.

So how does a device become waived? In addition to those devices that are automatically waived and those that are intended for home use, other tests may apply for waiver. To do this, the test manufacturer must demonstrate that the test is simple to use and is sufficiently accurate in the hands of the intended user, and according to the statute, waived tests are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result.

Most glucose meters currently on the market today, including those currently used in healthcare settings, have been cleared as home meters and have received waived status in that manner. We recognize the importance of having CLIA-waived BGMS devices in healthcare settings and understand why the use of capillary blood measurements in all hospital patients using an FDA-cleared and CLIA-waived BGMS would be more convenient and feasible for hospital staff.

We have been encouraging manufacturers of hospital-use glucose meters to seek FDA clearance and CLIA waiver for use in all hospital patient populations, including for patients receiving intensive medical care and intervention and therapy. Hospital-use BGMS devices are not intended for home use and would have to apply for waived status by demonstrating that they are simple and have an insignificant risk of erroneous results.

We would like to hear input from the Advisory Panel and the clinical community on

relevant factors that we should weigh in considering whether capillary blood glucose meter testing in intensively treated patient populations would meet the criteria for CLIA waiver, that is, that they are simple and with insignificant risk of erroneous results.

To close, our goals for today's meeting are to raise awareness about the observed accuracy of BGMS when capillary blood is tested in these patients receiving intensive medical intervention and therapy; to obtain advice from our Advisory Panel on this topic; and to hear public comment on this issue. Thank you.

DR. BREMER: Thank you.

And I'd like to thank both Dr. Landree and Dr. Lias for their presentations, and now I would like to ask anyone on the Advisory Panel, that we have an open floor for a -- if there are any questions or points for clarification that we can ask our FDA colleagues for.

Dr. Grunberger.

DR. GRUNBERGER: George Grunberger.

You mentioned a couple of times that you became aware of these datasets. Did anybody come to you? Or how did you find out about these things?

DR. LIAS: So people came to us and told us about them for various reasons, but they were not in a situation that was a public discussion or a nonconfidential situation, so that's why we requested permission to present the information. I can't disclose the type of scenario in which we saw the data.

DR. BREMER: Ms. Lee.

DR. LEE: Rosemary Lee.

Two concerns: One is that, of course, it's a lot easier for us to do a capillary blood glucose on critically ill patients. They get frequent blood draws, which leads to anemia, which leads to further requirement for a transfusion. So when you have a patient in diabetic ketoacidosis that needs every 1-hour blood sugars to titrate their insulin drip,

obviously, it would save, you know, drawing blood from the patient.

However, I'm also aware of some studies that have indicated that if a patient has even one hypoglycemic event while in the ICU, that it puts them at a higher risk of death, so the fact that the accuracy for hypoglycemia is not that accurate with capillary blood is a concern for me as an ICU nurse.

DR. BREMER: Ms. Kirkpatrick.

MS. KIRKPATRICK: Sherry Kirkpatrick.

To build on the hypoglycemia concern, in the emergency room perspective, neuro-deficit patients, seizing patients, we count on the capillary accuracy specifically for hypoglycemia. It takes time to get the lab venous arterial draw, so that is a concern.

DR. BREMER: Dr. Cassiere.

DR. CASSIERE: Hugh Cassiere. Just a question about the data: So they gave you a broad definition of these were just patients in a critical care unit; that's the extent of the information they gave you?

DR. LIAS: For two of the studies, we have a fair amount of information on which units, so some of them are presented for Study 1, and Study 2, we have that information. It's very similar to the types of studies used for the one meter that was cleared, so across medical, surgical, pediatric ICUs, and operating rooms, emergency departments, etc.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: Yeah, George Grunberger.

Courtney, as you mentioned, this has been in public discussions for at least 8 years, if not more. Are you aware, from discussion with the manufacturers, why is it so difficult either to do studies or to achieve the performance? Are there technical reasons? Do we know?

DR. LIAS: I don't know that I've heard discussion of why people would -- one, I

haven't heard before we saw this information. The reason we're presenting it is we were actually a little bit surprised at the consistency across three studies and two devices, and you know, we didn't actually really expect to see this based on the discussion that we'd been hearing from manufacturers and hospitals and researchers who study meters. So, you know, I think no one had generated datasets like this, you know, recently.

The discussion that you do hear is, yes, sometimes there are -- or that I have heard, so I certainly want to hear from you all, the discussion that we had heard that prompted the meeting and wanting to hear more from you all is, you know, some discussion of, yes, we all know that patients with low peripheral blood flow or DKA would have issues, but those are a minority of patients, and we can identify them and not test them. Those patients weren't included in this study necessarily, or they were assessed, you know, post, after the study to see are these the reasons.

And that wasn't the case, that they could identify -- if we just take out the people likely to have those conditions, the data improves. That didn't happen, so that was the other sort of reason we thought it would be helpful to present this and talk about it because we had heard more general discussions like that where we -- you know, people in the know, know who these patients are. I don't know if that is true or not.

DR. BREMER: Dr. Rej.

DR. REJ: In the documents prepared for the Panel, there was a summary of postmarket safety. Is that something the Agency could share here?

DR. LIAS: I can talk about that a little bit. So that's the MDR data, and that information is available online for everyone to see. So, historically, the glucose meters were cleared as home-use devices, meaning they used a product code. FDA has product codes to sort of categorize the devices for different tracking, and so if a manufacturer has an adverse event they want to report or a malfunction that they want to report, they would

report under that product code. It's the over-the-counter product code that they were using.

So you cannot distinguish in the dataset that we put there over-the-counter meters used at home, which are the vast majority of those meters, from the smaller population of hospital-use meters. Now, I will say the rate of reporting in hospital-use meters is higher than the rate of reporting at home, and there are so many more home-use meters that you still have a lot more malfunctions reported related to the home use.

So that data isn't terribly useful. Now, going forward, starting after our guidances were published, we will have a different product code for these meters, and so in the future, it will be easier to separate these out. Right now, you can't use it, so the data isn't terribly useful here. Unless you were searching for a particular instance or you knew what you were looking for, you could only find a particular instance where that had been identified as the reason, but it's not that helpful.

DR. REJ: Because this touches on the issue of unreasonable risk, I thought I would bring it up.

DR. LIAS: Right. It is hard to tell which ones of those are related here, though.

DR. BREMER: Dr. Nipper.

DR. NIPPER: I'm interested in the gold standard, if you want to call it that, method used for comparison in the lab, and I'm assuming that the studies that you cite used a consistent glucose method for either plasma or serum glucose throughout the whole study and one particular instrument or version of instruments. In other words, you didn't mix lab glucose methods, did you?

DR. LIAS: No. The --

DR. NIPPER: Or did they, I should say?

DR. LIAS: Study 1 and Study 3 used the same instrument, as our understanding.

Study 2 was at one site, using one laboratory comparison, so --

DR. NIPPER: Okay, and is -- and the relevant -- another relevant question is how did they ensure sample integrity from the draw to the lab? In other words, we all know that if you, if you haul samples in a van around the town or the county, sometimes there's sample integrity issues, so did they have good sample integrity control in the studies?

DR. LIAS: Typically they do. I think -- I don't know whether we have details on these studies, but these studies are performed similarly to others, and I would point out that the arterial and venous data were compared to the exact same comparator.

DR. NIPPER: Okay. Yeah. I'd just like to know a little more about the background and whatever's --

DR. LIAS: Yeah. So the arterial and venous testing was done by the same users --

DR. NIPPER: Okay.

DR. LIAS: -- and then compared to the same comparator.

DR. NIPPER: Okay, and were these glucose oxidase/hexokinase methods?

DR. LIAS: The lab methods, yes.

DR. NIPPER: Yeah, okay.

DR. LIAS: All the meters are --

DR. NIPPER: I'm not talking about the lab --

DR. LIAS: They're all glucose oxidase or --

DR. NIPPER: -- the lab itself.

DR. LIAS: -- glucose dehydrogenase.

DR. NIPPER: Yeah. The lab was using glucose oxidase or hexokinase? Okay. Yeah.

DR. LIAS: Or hexokinase, yes.

DR. BREMER: Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

I would like to get input from the FDA but also from other Panel members about international practice and experience in the same area, especially in the light of the fact that IFCC just published -- the IFCC Point of Care Testing working group, in the last couple of days, just published a document on this topic.

DR. BREMER: Do you want to respond to that?

And then Dr. Tung.

(Off microphone response.)

DR. BREMER: Okay.

Dr. Tung.

DR. TUNG: In our ICU the magnitude of the response to the glucose level scales with the severity of the abnormality. Of the 15% of measurements with the Machine A that are outside the 12%, where are those numbers? Are those very, very high, or very, very low? It doesn't matter if they're between a 150 to 200 band, but if they're outside more than 250, less than something, you know, if that's where all the abnormalities are, then that matters because we view insulin as a very risky drug, and any time we give it, there's a chance we could mess that up.

DR. LIAS: Yeah. That's helpful to hear. When we would have a submission in front of us, we would have all the data to look at, and in this case, we have summary. So we don't know that here, but I would say in similar datasets we see high flying, highly variable values in the outliers, and then also sometimes that are near there, but it's not limited usually to just near the cutoff cut points that we're using.

DR. BREMER: Dr. Wyne followed by Dr. Astles.

DR. WYNE: So I have a couple of comments, and I'm not sure if they fit here or later on, so I'll just bring them now.

In terms of what Dr. Tung was saying, in the hospital, he's absolutely right that part

of it is interpreting the glucose in the context of what's happening with the patient, where they were before and where we're trying to get them to. The two main situations in the hospital, I would say, are the person who actually has diabetes that we're trying to treat them, and generally, across the board, the hospital goal is around 140, which puts you into the range where these are accurate, in general, in the hospital. And then the other big situation is the cardiac surgery SCIP measure, which is the postoperative 6 a.m. value below 200, which also puts you into the pretty accurate range for these devices.

DR. LIAS: I wouldn't assume accurate ranges here --

DR. WYNE: That's true.

DR. LIAS: -- that then of above 75 doesn't necessarily mean that's driven by the hyperglycemic range. There is also error -- you know, you can have errors where the patient is really at 200, and it actually looks like they're at 100 or less, or the opposite direction. So, yeah, I wouldn't extrapolate that you know where in the range that's going.

DR. WYNE: But from a practical point, if you're trying to ensure the postop surg, CV surgery patient is going to have a plasma glucose below 200 on the 6 a.m. draw, using the glucose meter through the night to make sure your trajectory is downward is a reasonable clinical approach which we certainly use.

And what I wanted to raise is the approach our hospital took, and this wasn't specifically driven by diabetes, was, one, they now document every point of care, the source of the blood, whether it comes from capillary, venous, or arterial, so the person who's interpreting the value knows the source.

The other thing they instituted was what they called their BRAVE criteria, which is the person who's doing the sugar is supposed to assess blood pressure, reduced capillary refill rate, acidosis, vasopressors, or edema, and if those characteristics are there, then they're obligated to do arterial or venous instead of capillary. So we have a hospital-wide

policy that there's an assessment of the critically ill and the non-critically ill patient, and a decision is required to make of whether they do capillary or venous or arterial. And, to me, that's one way to mitigate the lack of accuracy that we all really want, so that's a consideration.

DR. LIAS: Yeah, thank you. That's helpful. I would like to hear some feedback on how widely understood some of these analytical issues are among the nursing and clinician staff in the hospitals.

DR. WYNE: So the one thing I would say --

DR. LIAS: It may vary.

DR. WYNE: -- about this is this really came from the critical care intensivists and nursing administration, so it's something that nursing administration is on board and the nurses are the one doing that assessment, and I actually first heard about it coming from them. I mean, I knew there was a committee talking about this stuff, but the actual determination and implementation, because it's coming from nursing administration, it's widespread, and there are even times where I've been asking a nurse, what is a sugar, and they say, well, you know, he met BRAVE criteria, so I'm waiting for the lab result.

And so in our institution, because of the way it was rolled out, there's been very good support and usage of it.

But I agree with you. The concern is most people don't know the accuracy issues, and that's a very broad concern, is how do we teach people. I mean, we have the structure that we've taught people in our hospital that they need to be aware of it, but in the national community, it's a big awareness issue.

DR. BREMER: Thank you.

Dr. Astles followed by Dr. Tung.

DR. ASTLES: You have so much good conversation I feel like my comment is behind,

but I did want to respond to Dr. Tung's comment and say that, just make out the obvious point that errors in these settings aren't Gaussian, you know, the mistakes, because they're typically point of -- they're typically unit use devices. They're designed so that you can't always know what the errors are going to be at the tails, just on what you know from the central tendency.

I wanted to ask FDA if they have any sense of where the errors were, whether they were negative or positive. Do you have the -- like the capillary, we know the capillary specimens were incorrect, but were they low and by how much?

DR. LIAS: In a submission, we could have that information. We don't have that here.

DR. ASTLES: Don't have it.

DR. LIAS: You know, sometimes -- I'm giving generalities, not necessarily these meters or these studies -- some meters do have tendencies to sort of have a bias in one way or the others. Other meters have a precision issue, and then if it's driven by some sort of patient condition, it may vary, so we don't have that information here.

DR. ASTLES: Thank you.

DR. BREMER: Dr. Tung.

DR. TUNG: I'll comment that in our ICU we don't even really trust any single measurement no matter where it comes from, so if we get a measurement that is errant by a point of care, you know, we'll make a small change and check it 15 minutes later with a blood sample, and if that doesn't look good, we'll check it with another sample, so there's, you know, a multi-layered set of safeguards to make sure we don't err in terms of intervention on a number that we think is abnormal.

DR. BREMER: Dr. Cassiere.

DR. CASSIERE: Hugh Cassiere. Just two quick points.

I think that SCIP measure's been eliminated, the less than 200 and greater than 200

for cardiac surgery, about a couple of years ago.

The other comment I'll make is that in our intensive care units, not just the cardiothoracic unit, we have a protocol where if someone is on an infusion of insulin, they're going to get started on an infusion of insulin, we do an arterial or venous sample and correlate it with the capillary just from the get-go. And then each day that patient's on an insulin drip, we do that calibration again, and the calibration that we use, and the number we came up with, and this is just arbitrary, is 15%, if it's within 15%.

The other comment I'd like to make is the elephant or the gorilla in the room is hypoglycemia. I've been doing cardiothoracic surgery for critical care for 22 years, probably over a 20,000-patient experience. Our tight glucose control predated the Van den data in the late '90s, and out of all that patient experience, I've never seen a patient die from hypoglycemia, although I've seen patients die with hypoglycemia, so I just wanted to highlight that.

DR. BREMER: Thank you.

Dr. Wyne.

DR. WYNE: So, yes, you're right about the SCIP criteria, but the importance of raising it was it heightened the awareness of trying to have a sugar below 200.

Again, back to what Dr. Tung said is he's absolutely right as we look at it in the context and we verify it, and I would suggest that probably any glucose below 100 is looked at as questionable, and we actually quite often get consultations for patients whose sugars are quote/unquote "hypoglycemic" because they're in the 70s and they're normal, healthy people who do not have diabetes, so that's a problem that we run into.

In terms of the cardiac surgery, you know, the Portland protocols predated the Belgium data, and that really was our first set of data that showed the benefit of glucose control in the hospital. And even then, in Portland, when they tried to target going below

100, they did run into too much hypoglycemia and so maintained the higher levels of sugar. But when you look at hypoglycemia in the hospital, depending on which data you look at, either the majority or a large percentage is completely unrelated to insulin at all.

And so that's a concern, and deaths related to hypoglycemia are usually not in a setting where insulin has been administered, so that's something that needs to be kept in mind.

DR. BREMER: Dr. Rej followed by Ms. McCollister-Slipp.

DR. REJ: Yeah. This is Bob Rej.

Following up on Dr. Tung and Dr. Astles's comments, the magnitude of the error -- this may not be a fair question because you may not have those data, but were consensus error grids or some error grid applied to the data from the studies that you referenced?

DR. LIAS: No. We don't typically use the error grids. They're pretty broad. The narrowest criteria on some of them are 20 percent, so they don't really give you the detail for the lower criteria, so we haven't used those. I mean, you could use an error grid on this, but I don't know that it would give you information beyond what's in those bins.

You know, the other thing is it's definitely helpful for us to hear, you know, if there are particular concerns when we would get some data on different magnitudes. You know, I've already heard the general comment that, obviously, smaller magnitudes are less concerning than larger magnitudes. But if there are -- you know, even though we don't have some of the details on the data, general comments or suggestions on what we should look at when we get to the questions later today, you know, it would be helpful to hear some feedback on that.

DR. REJ: Yeah. I'll go on record to say that I'm not a big fan of error grids, but I've given up that fight, but it would address that issue of is 100 mg low or high, depending upon the concentration. That's all where I was going with that. I think that would be helpful in

analyzing those data that are out.

DR. BREMER: Thank you. Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: A couple of points of clarification, just to make sure that I'm tracking: So I know that you don't use the names of the specific meters, which is fine, but were both of the meters referenced -- or I guess there -- were the meters approved for in-hospital use?

DR. LIAS: Since there's only three meters cleared for hospital use, I'm not going to answer that question because it would be a little difficult to keep them anonymous.

MS. McCOLLISTER-SLIPP: Okay.

DR. LIAS: Certainly they are interested and/or cleared for that use.

MS. McCOLLISTER-SLIPP: Okay. Because I have been hospitalized before where frequently --

DR. LIAS: I would expect this data is representative data of currently cleared meters.

MS. McCOLLISTER-SLIPP: Okay, and then towards the point of hypoglycemia and death, I mean, death from hypoglycemia is not the issue that was being addressed by the studies, or that wasn't being replicated; am I correct? Wasn't the death like all-cause mortality? It was just --

DR. LIAS: Certainly, if there were deaths, were known in the patients studied, they would be reported, you know, to FDA during the study. But, you know, these were analytical studies just looking at what the meters did, so in some cases, you know, the patient -- all of these patients had a laboratory value, so you know, you can't really -- the purpose of the study was not to follow outcomes. You know, a different type of study would be used to assess whether or not a patient managed with Meter X would have a good or a bad outcome. That wasn't the study that was done.

MS. McCOLLISTER-SLIPP: But in terms of the studies that you first referenced in

terms of raising the issue about the potential risk of hypoglycemia --

DR. LIAS: Those studies were designed to assess if you tried to titrate patients -- and most of these patients didn't have diabetes -- into certain ranges. Those were the studies that I referenced in my introduction. Yes. Those were different types of studies.

MS. McCOLLISTER-SLIPP: But the cause of death was not -- so when the Belgium study or the, I don't know, Dutch study, whichever study it was, was not replicated, the all-cause -- it was all-cause mortalities --

DR. LIAS: The study was stopped due to concerns of hypoglycemia that was leading to a higher rate of mortality. Right.

MS. McCOLLISTER-SLIPP: But it wasn't necessarily mortality specific to hypoglycemia; it was associated --

DR. LIAS: It was a higher rate of mortality, and there was a higher rate of hypoglycemia.

MS. McCOLLISTER-SLIPP: Okay, so it would be consistent with like the ACCORD study or something like that, where we did see a higher rate of death of people with --

DR. LIAS: It was a very large study.

DR. BREMER: Okay. We have Dr. Rendell followed by Dr. Tung followed by Dr. Grunberger.

DR. RENDELL: Just to follow up on a point that Dr. Tung has made, we talk about errors in absolute glucose values, but really the issue that we have to face is error in time, error in time to treat a critical condition. And the point, I think, that Dr. Tung is making is you really must have repetition in order to improve the quality of data and the interpretation of data, and that is a practical issue for nursing staff, who are often beleaguered simply by an order that a glucose be measured every hour. Well, that can translate into an error in time of up to 3 hours if an initial glucose point measurement is

missed and it is not until a couple of hours later that another glucose might trigger interest in a value.

So that we really should rethink the whole concept of point measurements, be they laboratory or glucose, and start thinking about the technologies we have been considering, which are continuous glucose monitoring, despite arguments about error in those measurements. There is great strength in repetition, great statistical strength, and 5 years ago I wrote an article where I predicted rapid evolution to continuous glucose monitoring in the hospital setting, and obviously, my prediction was not upheld, but 5 years later I still think we should consider the importance of repetition on statistics.

DR. BREMER: Thank you.

Dr. Tung.

DR. TUNG: I've been sitting here trying to think of the worst-case scenario in my head, and I imagine it would go like this, not so much the low glucose because our experience is very much like Dr. Wyne. If a patient trends even below 100, we would start double-checking and treating, but I imagine something like this. You get a finger stick and it says 300 but the real number is 200, but the 300 triggers a reaction, and so we give a dose of insulin. But we make a mistake on the dose and give too much because you can miss 10 for 100, and then the next thing you know, the patient passes out, and then you have to go check and chase it down and figure out what happened.

So it's even sometimes the high numbers that trigger up some more than the low ones because if we even start to see stuff go low, we would probably react to that more quickly than if they went, if they were trending high, so error at the extremes of measurement, those are very important.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: Yeah, thank you. George Grunberger.

As a clinician, obviously, I know what I want, and I know what should be perfect, and obviously, I agree with the suggestion for continuous glucose monitoring; you know, I'm a fan.

Let's go back to the politics, and I do feel your pain because you issued a final guidance, right, in 2016, you said, after very robust conversation with the stakeholders. We saw the data, and if this is all the data -- and, again, I recognize the problem. The question is do you have second thoughts about the guidance?

DR. LIAS: No. This isn't really about the guidance, from our perspective. Our main goal here is, one, we have data that probably may not be available or would -- might be available in a different form, and it's, we thought, helpful to share it with the clinical community, so that was our number one goal. Let's have -- make sure everybody sees this information, which hasn't really been generated.

You know, the guidance -- whether this meets the guidance or not is not relevant to our questions. We would really like to hear from the Panel what considerations we should make if we did get the submission, guidance or not, so definitely don't be constrained about the public discussion. We raise the public discussion merely to make the point that we don't think that people would have predicted this.

DR. BREMER: Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: So have you ever considered the possibility of maybe requiring, you know, at the extremes, whether they're high or low, perhaps if somebody tests using capillary blood tests at one of the extremes, requiring a second or third capillary blood test using a different digit or hand? Because I know that when I calibrate my blood glucose, my continuous glucose meter, if the number that I get is, you know, more than 20 points off from my CGM, I'll test -- and I usually do this when I calibrate anyway -- I'll test with different fingers and different hands, just to make sure that the level is consistent.

And it's frequently inconsistent. Sometimes that's because, you know, I may have picked something up with one hand versus the other, but it would be a way of sort of getting a better reference point just because of the variations in extremities.

DR. LIAS: One of the things we don't know is whether that would be true in this population or not, you know, whether there's something different about the blood, the glucose concentration in the capillary blood in these patients because of blood flow differences or whether it's user technique of collecting a capillary sample versus an arterial or venous blood sample. So that latter case, you know, you would see the similar thing that you may be seeing. The former case, you would get the same wrong result, so --

MS. McCOLLISTER-SLIPP: Well, I guess I --

DR. LIAS: So we don't -- I don't know that information, and then when the companies who did these studies looked to see if they could find patterns of types of conditions, they couldn't find any in these settings. Yeah.

MS. McCOLLISTER-SLIPP: Well, I can tell you -- again, this is *n* of 1 research here, but I've been doing it for 31 years -- that the consistency when I do that, if I'm calibrating and I just worked out or I've been walking around a lot, there is much more consistency between, you know, different fingers and different hands than there is if I've been sitting at my desk and writing or just woke up and I'm calibrating in the morning. So if you're in ICU, that could be a significant difference just in terms of blood flow, and there could be other, you know, types of issues in terms of how the patient's laying or something like that.

DR. BREMER: Thank you.

We have Dr. Lakos and then Dr. Cassiere, and then we will take a break.

Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

I think it's important to remember that not only extreme results can be incorrect or

inaccurate. Just because you get a normal result, that can be inaccurate too, so maybe you get a normal result, you think it's fine but missing the intervention; it can be the same amount of error of, you know, doing the wrong intervention, so unfortunately the error is random.

DR. BREMER: Dr. Cassiere.

DR. CASSIERE: Hugh Cassiere.

So I guess we're talking about is we're talking about a broad patient population. I'll give you an example: So I could have a patient in Bed 1 who's postop CABG, extubated the next day, getting finger sticks. Am I going to be comfortable with the potential of an 86% inaccuracy on that patient? The patient in Bed 2 I have on ECMO, who may get a heart transplant or an LVAD, am I going to be comfortable on any inaccuracy with a finger stick on that particular patient?

So I bring that up because we're talking about intensive medical patients who are getting care, and there is such a broad range. And all these patients, you could even make argument that the patient who's post-CABG probably has some capillary filling issues as well, but I guess the comfort with inaccuracy on that patient would be a higher than that other patient that I mentioned. I throw it out there for the Panel to discuss that.

DR. BREMER: Great. I want to thank the Panel for this discussion. It's been extraordinary, and to stay on track and stay on program and be a good Chair, I'm going to -- I will grant a 10-minute break.

Panel members, please do, during the break, think about the questions posed to us by the FDA because I think that's the strength of having everyone here at the table, but that said, please do not discuss the meeting content during the break amongst yourself or members of the audience.

We will break now for 10 minutes and resume at 9:40. Thank you all.

(Off the record at 9:30 a.m.)

(On the record at 9:45 a.m.)

DR. BREMER: Welcome back, everyone. Thank you, and thank you for staying on time. It's now, for the record, iPhone says 9:45. We'll resume.

I do want to open the floor to discussion from the experts around the table to begin deliberating on any issues that you may have with the data you have heard today, either in the Panel presentations, the discussions with the FDA, or the material that you read in your packets prior to the meeting, and I do want to thank our FDA colleagues for giving us the information for us to review prior to the meeting.

I also, as we have discussions in the next hour or so, I kind of challenge the Panel to really think about the questions posed to us by the FDA. The Question 1 really was regarding are there risks and benefits of using capillary blood glucose measurements in the hospital? What are those? Can we better define those? How do we use the data? How do we mitigate the potential risks? How do we practically provide constructive feedback to the FDA, moving forward, with the use of capillary blood glucose in hospitalized and intensive care managed patients?

And also for that matter Question 2, which is another issue about the issue of CLIA and CLIA waiving of devices and the use of self-monitoring, those devices in the hospitalized setting. I think, again, we have a tremendous group of experts here at the table, and I appreciate you all being here, and I think, collectively, I'd like to, at the end of the day, to provide the FDA with some constructive advice and feedback on those questions in particular.

I also would like to iterate that although this portion is open to public observers, public attendees at this point may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves

each time. I'll try, up here, to announce your name, more so for the transcriptionist and for the public record, so as people review these documents, we know who was speaking.

So, with that, thank you for coming back and not running for the door, and I open the floor to the Panel.

Dr. Rej.

DR. REJ: Okay, somebody needs to start.

So although this meeting is about blood glucose meters, I think the overarching issue is sample type for any medical device. And I was wondering what the opinion of the Agency is, that if a certain sample type were shown to be usable or not usable, or an analyte, would a device that is cleared for a different sample type be able to be used for the alternate sample type? In other words, that if I were to show that capillary blood from a certain group of patients is identical to normal capillary blood -- capillary blood from a normal individual or from venous or plasma from a normal individual, would that be transferable to any device that uses that sample type that's been cleared for venous blood?

DR. LIAS: Courtney Lias.

I'm not sure I understand your question.

DR. REJ: Yeah.

DR. LIAS: But inherent in it may be whether or not some properties might be transferable across devices.

DR. REJ: Correct.

DR. LIAS: Is that what you're asking?

DR. REJ: Yeah. Correct.

DR. LIAS: So --

DR. REJ: For example, in the examples from the large studies that the Agency presented, it showed that there is just a different performance of the identical device in

two sample types. If another study were to show that a different sample type was identical to the original sample type, let's say venous blood, would that be applicable to that device? Or would another study with that device -- and would every device need to do that study, or is just one study necessary to more or less clear capillary blood from a certain patient set?

DR. LIAS: So it does depend a little bit. So in some cases, for devices in general, you can transfer sort of properties of testing across devices, so the maybe easy example might be we don't make people prove that it's useful to do sodium testing, you know, every time you come in with a sodium test. We look at how well that sodium test works in the samples that you're claiming, but we don't ask them to show us why you would test sodium, so that information is referenced because it's generally applicable to sodium.

In another case, troponin, each troponin test actually has different performance. They're not standardized. You might get a different value across troponin tests, and so they have to do bigger clinical studies to demonstrate the performance of each troponin test because you can't transfer the clinical performance of one troponin test to the clinical performance of a different troponin test.

And then in the case of sample types, if there's something generally scientifically known about a particular sample type, certainly that information would be taken to account when you're looking at what types of studies might need to be done, but it depends a little bit on the device and the scenario as to whether no studies would have to be done or some studies would have to be done.

For example, if there are small differences in performance across devices that might be more easily detectable in certain scenarios, you might take that into account but -- so I can't answer it for sure, but certainly where it's a physiological parameter that's understood and predictable, that makes it a little bit easier to incorporate.

DR. REJ: Okay. The reason that I ask it is that in some of the data that was

presented, it showed that one of the devices, I think it was Device B, was equivalent in venous blood and capillary blood from normal individuals but was not for those that were in intensive care or some hospitalized subset.

DR. LIAS: Courtney Lias.

We didn't present venous blood on Meter B. We only presented capillary blood in ambulatory population versus, just to clarify, to capillary blood in the intensive care population.

DR. REJ: Okay. Thank you.

DR. BREMER: Dr. Cassiere.

DR. CASSIERE: Hugh Cassiere.

So I guess we're talking about -- and my last comment is when would we tolerate a test that's less accurate in our particular patient population? And I think that's what really comes to my mind. When would I tolerate a test that's not 95% accurate but 85%? Under what circumstances?

And I'll throw on top of that a test that you're going to be performing serially, so if you have someone on an insulin drip and they're on q 1 hour, are they going to have at least -- some of our patients get tested even in a half hour, depending on what the glucose is, so you're talking about a test that has an 85% accuracy with capillary blood on a test you're going to be performing anywhere between 24 to 34 times a day.

And I want to put that in context because we're not looking at an isolated -- you know, I'm going to step off on what Dr. Tung said; we're not looking at an isolated number. We're looking at a continuous variable over time, and I think that's very important.

DR. BREMER: We have Dr. Wyne followed by Dr. Grunberger.

DR. WYNE: I want to just say something related to what you just said, because you're absolutely right as, you know, how much are we willing to tolerate. But whatever

the decision is, it also has to be that everybody involved in the field is aware of that and is made aware in a way that they can be confident and safe in what they're doing. So they're two different things, but one absolutely follows from the other. And I think that's something actually Courtney raised, which is we need to make sure people are really aware of what the error is in these devices and then teach them how to feel safe with it.

I don't think that's FDA's job to teach them, mind you. I'm not saying that, but we, meaning as a medical community, we have to do some kind of awareness and education that goes with it once it's established.

DR. BREMER: Dr. Grunberger followed by Dr. Nipper.

DR. GRUNBERGER: Yes. Thank you.

Yeah. I mean, you started, I guess, the relevant part of the discussion that you sort of try to distill it. We have basically two choices. One will say that the results given to us are just not good enough, and so let's wait until there's something on the market which gives us results which satisfy the criteria or deal with the reality. This is what we have today, and as clinicians, we have to decide what will be the general guidance which can be understood across, I mean, all the hospital settings. That is, do we define certain populations and certain units in hospitals for which the capillary testing with the current device is fine because the risk might be lower? Or do we define a certain level glucose below which we'll have to do some additional testing or determine the frequency of testing, but it has to be something which is generally understandable and applicable across the whole country, because otherwise it's going to be more complicated and it will just confuse everybody.

So I think the question is do we go by population? Do we go by glucose levels? Or do we just forget the whole thing and say that nothing is good enough, and let's ask manufacturers to come up with better devices? Right. I mean, I think that's the gist.

DR. BREMER: Dr. Nipper followed by Dr. Astles followed by Dr. Lakos.

DR. NIPPER: I'm responding to Dr. Cassiere and Dr. Wyne. Henry Nipper.

One of the things that I'm hearing as a clinical chemist for many, many years is a merger by the discussion, several of the discussions of accuracy and precision as error. And I would want to point out to the group that if Dr. Cassiere's patients that he's monitoring every half hour have a device that's being used that has a high imprecision rate, you're going to see dramatic shifts in the glucose up and down, which you have to deal with and understand what to do about, if what to do about it is nothing.

I think we have to separate accuracy and precision here in our discussions of error. Bias or the inaccuracy of the meter, if it's a highly precise meter, can be calibrated out and can be, in physician judgment, can be used to adjust therapy based on the recognition there's bias, but I don't know how much of the error we are seeing is imprecision. Imprecision comes right back to what Dr. Rej is talking about in that capillary draws can be highly variable in quality and cannot correlate well with a venous or arterial stick.

And I see Dr. Lias is eagerly wanting to jump in here, so I'm going to stop.

DR. LIAS: Courtney Lias.

No, I definitely agree that those two issues should be distinguished, and I appreciate you bringing that up. I would point out to you that this precision thing would be easier to catch in my opinion. The bias thing, if you had a bias that's caused by the patient and not the inherent meter, then the serial monitoring would not catch it, so you might have a patient who looks normal who's not normal, who would also look normal the next time you tested them.

DR. NIPPER: And this is Nipper.

I agree with you, Dr. Lias, but still, if you have clinical criteria that you can use to tease out the patient that might have the bias, I mean, this becomes a very difficult track to

go down, but I think that, I think we're onto something here.

DR. BREMER: Dr. Astles.

DR. ASTLES: Yeah. Great conversation. Along the terms of bias versus imprecision, I'll just say that, you know, a patient might start with no bias and then have increasing peripheral edema, and I understand, I appreciate the value of Dr. Wyne and others who have said that, you know, the value in doing these kind of assays is serially over time so that you could look for a trend, so just a different way to look at bias that may change over time due to change in the clinical condition.

To me, it seems that the greatest issue is not the glucometer devices, because they're pretty good using venous or arterial blood. They've done quite well and do well. It's the intersection of the sample, capillary sample among certain groups of patients. For some patients, capillary samples are fine.

So I just wanted to reiterate what I think we all intuit, which is that it's probably not going to be possible for industry to better design devices for these particular patients that have, that we want to get capillary specimens on due to timing, unless -- I think that's always going to be a problem. Thank you.

DR. BREMER: Thank you.

Dr. Lakos.

DR. LIAS: Gabriella Lakos.

So along the same line, I was trying to kind of narrow down this issue. So we were talking about accuracy and precision, and I would like to agree with Dr. Lias that the instrument by itself, analytically, is precise and accurate. If you put it on a bench and test it, it's precise and accurate.

I would also argue that the issue is not only with the capillary sample, although there are more issues with capillary sample than venous sample, as we all know, but again, if you

isolate the issue, the capillary sample itself is not the problem. The problem is the condition of the patient, which is changing, which is unstable, which is unpredictable, so what we need to isolate here, what are the conditions or what are the situations where we limit or don't limit the use.

And, honestly, here I am struggling because those patient populations that would benefit the most from this technology may be, need to be excluded because of the unstable conditions like hypoxia, shock, or blood pressure, or any other issue. So, basically, if we consider what can influence these results and what makes it unreliable and we include those populations, we include the population that would benefit the most, so here, I'm struggling a little bit.

And from that point of view, actually I also wanted to bring it up, it almost brings us to what's continuous glucose monitoring, where not just a point of time estimate but the trending would give you that additional information that would help you make clinical decisions. And I know it's the future, but I think we should talk about that.

DR. BREMER: Dr. Astles.

DR. ASTLES: I'd just like to thank you for pointing out that my analysis is shortsighted because it is the patient factors as well, that they may be on drugs like ascorbic acid and things like that, which these -- which patients -- and any other drugs, which patients outside intensive care units might not be on, so it's not just the specimen type. Thank you.

DR. BREMER: Thank you.

Dr. Cassiere.

DR. CASSIERE: Hugh Cassiere.

So you're right; it's about the patient, and it was enlightening to point out the devices are accurate and precise. It's the sample, and that sample is going to change

depending upon the patient characteristics. Then that gets thrown into the clinical realm, right, Dr. Wyne? So you made mention before how they do blood pressures and assess for peripheral perfusion. Some of this needs to be in the clinical arena, when to use capillary blood and when not to.

And we could probably all come up with -- I have at least 10 things in my head I can say when I would not use capillary blood, but that patient may change over time, and that's the hard part. And I think that's why we can't clearly put this into a little cubby, because that patient that I told you who was on ECMO going for a heart transplant, maybe 2 days they're on an LVAD and I can use finger sticks, so it's really the clinician needs to make an assessment, do I feel comfortable with capillary blood? And that can be based on hypothermia, what pressors they're on, are they on renal replacement therapy. You could think of a whole bunch of things.

And that's what we're going to have a hard time coming up with to make that list, so then it needs to be education and make the clinical community aware of all the pitfalls that go along with capillary blood sampling.

DR. BREMER: Thank you.

Dr. Wyne.

DR. WYNE: I have a question, and it's simply because I can't remember this number from back when I was in training and taught this. And I totally agree that it's the patient, but when you do a finger stick glucose, I was taught there is a difference in the accuracy if you use the side of the finger versus the pad of the finger, and my specific question is does anybody remember what that differential is?

And the reason I'm asking is, is that differential sufficient to make a difference on whether someone's hitting a 10, 12, or a 15? And I'm asking that because what I do in our hospital, not just my current one but previous ones, is I watch them do the finger sticks, and

many people get very angry when I correct them in telling them that they're doing it wrong, especially the person whose sole job is to do finger stick glucose in the ICU.

But I just can't remember what's the differential by those two sites, but I know there is a difference, and I don't know if anybody here knows.

DR. BREMER: Mr. Aviles.

HSCM AVILES: Mike Aviles.

As an end user, as a paramedic and in the prehospital setting as well, the understanding I -- as I understood it in my training was that the side versus the center was more of the hardness of the skin around it, and then the other thing was the pad area was just a little easier based on the type of probe you would use, and so that's -- that was, that's one understanding. The differences between them, I think that was also something that was done a few years ago, versus now where it's taught the center is just as good as the side, as I understand it.

DR. WYNE: So my recollection of the original data was that there is a differential and it has to do with the capillary network and the perfusion of the side of the finger as opposed to the center or the pad of the finger, so that's why I'm asking the question.

DR. BREMER: Dr. Nipper.

DR. NIPPER: Henry Nipper.

I don't think you can put a number on it, but I can tell you that as the sticker and as the stickee, as the stickee with sepsis in the hospital, having the tight glucose protocol run on me, I've had to teach the person taking the glucose how not to milk the capillary out, because it changes the cellular fluid, extracellular fluid ratio. It screws up the number, and so there are so many things that can do this, that can mess up this, whether you stick the pad or stick the side of the finger or stick somewhere else on the body, as far as I know. I've never had that done.

But I think this is a -- we're coming full circle back to Bob Rej's comments about capillary fluid sampling is an art. It is not necessarily standardized. It's not necessarily widely accepted that one technique is better than the other. And maybe in all facilities we don't have standardized capillary sampling techniques, and I think that's something we should try to focus on in the future as a group, not necessarily FDA group but as a group of people who are trying to improve patient care.

DR. WYNE: Okay. Can I ask a question? Is it possible to ask if there's anybody in the audience who has expertise and knowledge of whether technique matters? Is that a -- can we do that?

DR. BREMER: That -- I think any of the discussion that can be informative -- I don't want to --

Ms. McCollister-Slipp, we'll get to you next.

But I think, in the spirit of this discussion, if there is input from the audience, we'd be happy to hear it.

(Off microphone comment.)

DR. BREMER: Actually, if you wouldn't mind please coming up to the microphone. I appreciate your bravery in coming up, and now I'll ask you also to state your name for our records, if you will, and affiliation.

MS. BOGNER: My name is Deanna Bogner, and I am here just as a member of the public. I paid my own way to come, so --

I am a point of care testing coordinator and have been teaching this for 20 years. There was a time that it was taught to stick in the middle of the finger, and some people still do that, but essentially, make a smiley face on your finger and don't stick where -- and stick where the nose is. There's less pain there.

I teach side of the finger. Press hard with the lancet until you see the capillary refill,

then stick, because the needle depths are different and you do not milk like a cow, so it -- the teaching for the point of care person versus what the nurse 20 years ago learned in nursing school versus what the actual practice is for a new grad that sits in my class is totally different.

MS. McCOLLISTER-SLIPP: But -- this is Anna McCollister-Slipp.

But what's that based on? I mean, again, I've got -- I've been doing this for 31 years. I've got lots of calluses. I mean, I go with where I can get blood to drop from my finger at that point in time. And, you know, if I've been working out, it's pretty easy, but otherwise -- I mean, I use the side frequently because there are less calluses, but I think part of what we're trying to consider here is, is your teaching based on understanding of where the calluses and the nerves are? Or is it based on an understanding of are there any variations in the accuracy?

DR. WYNE: Just a moment before you answer. The important point that Anna is -- I totally understand what you're saying. You live with it; your fingers are callused. But the point here is the science of how do we use the device in the most accurate way, which is not always real-world experience. We know that.

DR. BREMER: Yeah. I want to jump in here as far as procedurally. I appreciate the audience in the line because then that shows engagement. Since we're not in the open public session at this point, what I would like to -- don't go away. I would like comment, though, on the actual procedure, not necessarily opinions or rather reflections of what should or shouldn't be done, but as far as the actual procedure of capillary blood testing, we will entertain those now. Other comments, absolutely, at 11 o'clock we'll entertain them. Thank you.

MS. CLARK: I'm Silka Clark. I'm the point of care manager for Children's Hospital in Colorado and previously for Centura Health Network, and I just wanted to add to what

Deanna said. We always teach to waste the first drop, test the second drop as well, so we do access the side of the fingertip. Never test that first drop. Always waste it with a dry piece gauze; test the second drop.

We also have a fail-safe in our interface manager to kill the first one if they do two within 5 minutes of each other and only chart the second one, so we've kind of got a built-in self-destruct mechanism if they see that first one doesn't look right.

DR. BREMER: Thank you.

DR. KLONOFF: Hello. I'm David Klonoff, Medical Director of Diabetes Research Institute at Mills Peninsula Medical Center in San Mateo.

So the question came up: Is there a difference between the results when you stick the finger in two different places? I reviewed this literature very carefully. I've never seen a paper that addresses this, let alone shows a difference, so it's sort of like proving a negative. I don't think there's any evidence that there's a difference.

DR. BREMER: Thank you.

UNIDENTIFIED SPEAKER: You answered -- you made my comment.

(Laughter.)

DR. BREMER: Perfect. Okay. Well, we'll get to Mr. Aviles. Just procedurally, for the record and for the public comment, any questions directed to the public, please go through me. That way there's a clear chain for the transcript.

I want to thank the audience for the points of clarification and to briefly summarize before I turn the floor over to Mr. Aviles. As that, the answer to your question probably is unknown, and there is myriad techniques that are both taught, employed, utilized, or received. Okay.

Mr. Aviles.

HSCM AVILES: Yes, sir. Mike Aviles.

I'm just going to reiterate that point is that it's mainly user preference and what the institution is teaching at the time, and we can maybe state that a consensus is, is that there is no true scientific method at this point.

If I may continue, just a question regarding the sampling during the study: Was there any record of -- or that documented maybe error rates on the device or the user or the operator that was taking the sampling? Was any of that ever tracked?

DR. LIAS: So we don't have the details on these studies, but you know, we would typically have the types of users that were used, and depending on the study and how it was conducted, they may have a lot of detail on exactly which users did which patients. Most often they do. In some cases they might have more general information to share. They also would have information in these studies we would request on patient conditions, drugs, you know, the site in the hospital. They would analyze to see if there were differences across hospital sites. They try to look as well as they can across conditions and medications, though often those sample sizes are small within those subgroups, so it's kind of hard to tell a little bit.

So, you know, in devices, we're very accustomed to trying to label information that's helpful, but you would have to know how to identify which populations to label.

DR. BREMER: Thank you, Dr. Lias.

In the spirit of stimulating the discussion, I'd like to take just a second and, as Chair, and summarize, and what I'm hearing is that there's many moving factors, but the source of the capillary blood glucose in a clinical patient may evolve and change over time. And it is very difficult to categorize risks and benefits and what patient population should or shouldn't be evaluated with capillary blood glucose levels. And I think that does, that does kind of evolve into Question Number 2 that was posed to us as a panel, to provide some guidance or consideration about the use of capillary blood glucose in self-monitoring of

blood glucose meters in certain settings as a CLIA-waived, as a -- in a CLIA-waived fashion, and I'd like to get the input on the Committee about thoughts on that.

Dr. Cassiere.

DR. CASSIERE: Sure. So what I would at least recommend is highlighting the inaccuracy of capillary glucose monitoring in the critical care population, just as an education for the clinicians and to let -- raise that level of awareness, that if you have an institution or a unit that's using tight glucose control, which probably shouldn't happen anyway, that you need to be cognizant of the fact that you're going to get inaccurate readings on this patient population, and you need to have some mitigating factors or some criteria for patients who are going to be followed with capillary versus venous or arterial blood sampling.

DR. BREMER: Thank you.

Ms. Kirkpatrick.

MS. KIRKPATRICK: Sherry Kirkpatrick.

And to continue on what Dr. Cassiere's -- it truly would be a burden at the bedside not to have the waived point of care testing. So I think disclosing the inaccuracy possibly of capillary, maybe going back to the sample collection, but most importantly, I think, in the critical care setting, stressing the importance of venous or arterial blood collection would be key for accurate sampling.

DR. BREMER: Dr. Lias followed by Dr. Rendell.

DR. LIAS: Courtney Lias.

It would help at some point to understand how this information might best be addressed by FDA. The label doesn't tend to get to the end user. Usually the laboratory has the labeling of the device, traditional package inserts at least, and maybe the point of care coordinator may have it, but not typically the user, so it would be helpful to understand

ways that FDA should consider disseminating information in terms of labeling. And labeling is an actual official term for devices, meaning any information accompanying the product.

DR. BREMER: Thank you, Dr. Lias.

Dr. Rendell.

DR. RENDELL: Sherry Kirkpatrick has made a comment about burden, and it is truly remarkable how a critical care nurse can function in today's critical care unit where you have a patient, they have three different IV lines running, they have an oximeter going, they have their electrodes for their EKG and their ambulatory blood pressure monitoring going, and they're being asked to do individual point of care glucose values. We really can't start thinking about single errors in one reading. We have to do what was just stated. We have to get more frequent values, and the best way to do that is to start the FDA pushing for continuous glucose monitoring in the hospital setting, even though that is a very large task. We have every other probe on these patients, and adding a patch on the arm which can easily be scanned is a reasonable prospect for the future.

DR. BREMER: Dr. Rej.

DR. REJ: Yeah. This is Bob Rej.

Commenting on off-label use, I'm not certain how the studies that the Agency presented earlier this morning were done, but given the nature of the type of errors we're seeing with capillary blood taken from a certain class of patients, I'm not sure that it would matter very much whether that were done in a waived setting or in a high-complexity laboratory. It's not so much a condition of the device and the oversight; it's the nature of the sample.

DR. BREMER: Ms. Lee.

DR. LEE: Rosemary Lee.

I just want to concur with Sherry in regards to the education. You know, my staff

think that I'm very smart, but I did not know that there was such a variability in the capillary, so I don't feel so smart. And so I think you're correct; the end user needs to be educated as to the variability of the glucose levels, especially with hypoglycemia, so that's one thing that needs to be reinforced.

And then, also, if we could come up with a continuous glucose monitoring, that would be wonderful because my staff is always crying over the fact that their little fingertips are all little pincushions, especially when they have a prolonged ICU stay.

DR. BREMER: Ms. McCollister-Slipp followed by Dr. Rendell.

MS. McCOLLISTER-SLIPP: So question for Courtney, or Dr. Lias, sorry.

What kind of -- or I guess the question is do you have requirements for manufacturers who have point of care approvals or, you know, machines that are approved for point of care? I mean, do you have requirements that would ask them or force them to provide data about variability in different patients in different types of settings? And are the studies big enough to even conclude what kind of variability might be present?

DR. LIAS: This is Courtney Lias.

There are general requirements for providing adequate instructions for use, which -- and then some other sorts of labeling requirements for in vitro diagnostics that include descriptions of performance. There are also certain requirements related to intended uses. So, yes, when you put them all together, manufacturers have to specify what they intend their device can be used for. Specify appropriate limitations of that device. Specify who the -- the performance of the device in those populations.

And then, you know -- but like I said, most of the time that information is in the package insert, which accompanies the test. In the case of a meter, there's a package insert for the test strip which contains some performance information, but that's with the vial of strips or with the box that the vial comes in. The meter manual is usually probably just kept

somewhere. It's probably not laying around and read very often and things like that. So there are different types of labeling. There are certainly -- sometimes devices also have, you know, on-device labeling and things like that.

But to answer your question, yes, manufacturers should study the device and the intended use population and describe its performance and appropriate limitations, and the form that takes really depends on what the situation is.

MS. McCOLLISTER-SLIPP: Like so, for instance, in this case -- this is Anna McCollister-Slipp again -- and if we're looking specifically at people in the intensive care setting -- actually, you know, my father has Type 2, has had it for almost as long as I've had Type 1. He literally just had his second major stroke in the past month and just was moved out of ICU. He's been insulin dependent for years, and I just texted my sister to see what kind of blood glucose testing they'd actually been using for him.

He is incredibly sedentary and has been for quite some time. I would imagine that there would be significant variability between -- you know, based on my personal experience, just as a very different patient, I would imagine there would be significant different variability in the different hands and fingers and --

DR. LIAS: Right.

MS. McCOLLISTER-SLIPP: Is any of that required for submission for that kind of an indication?

DR. LIAS: This is Courtney Lias again.

If the Panel finds it valuable to try to identify certain groups of patients that could be handled differently within instructions for use, that's fine usually. You know, you can say in the labeling, do this in this case, and do this in this case, and do this in this case; however, the more complicated it gets, maybe the harder it is to fit into clinical practice, so there's considerations there. But one of the challenges here is that, at least currently, we do not

understand which patients you would describe.

So, you know, we would be happy to hear feedback on that point.

DR. BREMER: Dr. Rendell followed by Dr. Cassiere.

DR. RENDELL: Yeah. In many cases, patients who do not require intensive care are shipped to intensive care, and the typical patient is a patient in whom one wants to perform an insulin drip. Well, the nursing staff immediately says we cannot perform an insulin drip on the floor because we do not have the staffing to do the glucose testing on an hourly basis, or even on a 2-hourly basis.

So we have to think about the reality of what we are requiring from the nursing staff in terms of these point of care glucose measurements that, whether they are accurate or inaccurate, are an issue in time and an issue in treatment.

DR. BREMER: Dr. Cassiere.

DR. CASSIERE: So, again, we can come up with a list of patients who are at risk for using capillary blood. You know, we can make a list of hypothermia. But why not recommend, if you're going to use capillary blood sampling, to at least correlate it, either the first or second time, with the venous and arterial, and if there is a -- pick a number -- 12 mg if it's less than 75, or 12% if it's greater, then it's safe in that patient, or at least you can mitigate the harm, because every -- I can think of a few patients who are hypothermic that capillary blood may be good and some patients that are not.

So picking specific diseases, you're going to have variability, but if you correlate it with the gold standard, then at least you can fall back and say, I feel comfortable with this capillary blood sample.

DR. BREMER: Dr. Tung followed by Ms. -- Dr. Lakos.

DR. TUNG: I would say, with respect to awareness and education, there is a critical care literature comparing point of care with arterial and venous in the ICU. I count at least

five studies published since 2005 and even a systematic review in 2013. The general consensus of all of those papers is that it's not accurate, and one should be careful when using that kind of sample.

So an intensivist trained within the last 10 years, I imagine, should be aware of the inaccuracy of these monitors when using critical care setting.

DR. BREMER: Dr. Lakos.

DR. LAKOS: I would like to add to the correlation with the gold standard method, in my opinion, it's true at that point. It may not be true half an hour later, so I don't -- that's the issue, that the condition of the patient is changing. I think that's the challenge.

Regarding the risk mitigation, I mean, if we consider what are the situations or what are those conditions that pose a higher risk, I think, at least for couple of them, we can propose mitigations. In an intensive care setting, the blood pressure is available. The patient is on monitor, so it can be obtained. We can set limits that within -- or beyond certain ranges we don't use it. Temperature is available.

I would like to point out another factor that influences capillary glucose results, and that's hematocrit, and that may be potentially -- and I challenge the industry. I am from industry myself. Maybe we can think creatively, and maybe we can develop a software application where you can actually input the hematocrit value, and that corrects the capillary value. It's an idea, and I don't know if it has, you know, merit. It needs to be tested, but at least one factor can be compensated for, and many others can be detected.

DR. BREMER: Thank you.

Dr. Lias followed by Dr. Cassiere.

DR. LIAS: Dr. Courtney Lias.

So, Dr. Tung, it's helpful to hear that the guidelines, you know, may exist cautioning about capillary blood use. It would be helpful for us to hear a little bit more about that in

terms of, you know, what that would mean for the Panel's recommendation. So, for example, are the recommendations such that they caution against using capillary blood, that they caution on how one would interpret capillary blood, and what would that -- you know, consider when you get to our questions what would that mean for whether FDA would determine that the device is as safe and effective as other medical devices for that use or not.

DR. BREMER: Thank you, Dr. Lias.

Dr. Cassiere.

DR. CASSIERE: Yes, so just -- I'm going to mention something about that.

But we have patients who, if you take a look at hemodynamic parameters, they look like they're hemodynamically stable but they're in shock, so I'm going to go back to that. We're not going to be able to come with a list for the FDA to say if they have A, B, C, and D, so now we have to have a fallback.

The two issues are -- and Dr. Tung brought up, there's literature in critical care. We've known for years that capillary glucose or point of testing is unreliable. We know that, and yet we still do insulin drips in the intensive care unit, and the glucometers are invaluable, invaluable pieces of equipment to help take care of that patient.

But we also have to throw into there how do we mitigate what is the -- there's untoward effects of hyperglycemia. Hyperglycemia is not going to kill you in hours. You may have some untoward effects over days to weeks, but hypoglycemia will kill you in hours or even in a couple of hours. So how do we mitigate the hypoglycemic effects, and this is with or without insulin, with measuring capillary glucose with these devices?

And I can tell you just from clinical practice, if I have a patient who's, for lack of a better term, clinically unstable, we are not using capillary glucose to manage that patient. Most patients who are in the realm of in shock usually have arterial catheters or central

lines for invasive monitoring. We don't use capillary glucose.

But when that patient gets better 5 or 6 days down the road, and they're extubated and out of bed to chair and they're weaning on, they're almost off their pressors, I'd like to use the capillary, so it's one of those moving targets devices on -- we're not really talking about a device. We're really talking about where the sample comes from, and we've so far disconnected the conversation between the glucometer and the finger stick. How do we grapple with that?

It's not the glucometer that's the problem. It's the sample and the stick. How do we regulate that? Do we need to do both? It's all going to be education, but again, I want to highlight we're not going to be able to pigeonhole specific diseases or diagnoses to say stay away from capillary perfusion. It's going to need to come down to the bedside clinician, and we need to educate them.

How do you translate that into education? One of the things -- again, I'll go back to doing a sample at the same time. I take care of critically ill patients all the time. There are a handful of patients that are okay an hour, and 2 hours later they're dead. Very few of those patients -- and those are the patients, when they get to that point, I'm not using capillary glucose anyway, but if I want to use capillary glucose continually and the patient's stable, well, at least I'll know it correlates with the venous and arterial sample and I can continue that glucose management, insulin management afterwards.

DR. BREMER: Thank you.

Dr. Wyne.

DR. WYNE: So I think what I'm hearing from you is you're suggesting it's not that the glucose meters cannot be used in the hospital for capillary glucose; it's that there should be some kind of guidance on how to make the proper clinical decision of when to use capillary versus venous and arterial and, more specifically, that you can't just say ICU, non-ICU. And,

absolutely, I know patients who have poor perfusion or are very swollen, and they're outside the ICU, so again, it goes back to the question of what data do we have to create some kind of clinical criteria? Or is there something that FDA could use as a reference to make such a recommendation?

And part of why I'm saying this is summarizing it as this is kind of the way I think of it too, that we know there are situations where it's not safe to use it, but do we actually have it codified? But at the same time, are we here at this table willing to say, for the patients who are not in that clinical scenario, we feel safe with the currently available meters?

And then, of course, I have to take it one step further and say, you know, one way you could do it is at least we have our BRAVE criteria that could potentially be used as a way to identify that patient, and that at least gives you some specific clinical criteria to use as a framework for decision making. But I don't know that there's any formal data or outcomes or if there's even meant to be a data analysis of that.

DR. BREMER: Dr. Tung. Thank you.

DR. TUNG: I was going to say I imagine that one reason that this question is being raised is because of the burden on hospitals for off-label use of point of care glucose measurements, and once you lay down criteria, now the hospital has a different burden, to show that they're following those criteria. You know, I'm not sure, given the quality of the data that we have, that you're making things better for that hospital, so I don't have a good sense of the pressure from the hospital side that this is an issue that would be solved by a set of rules.

DR. BREMER: Thank you.

Dr. Lias.

No. No, no. I thought I saw a hand, but I guess I'm going to jump in, and also -- this has been a great discussion, and I'm going to push us again also based on kind of the second

question we've been asked to ponder is we've had the discussion about the potential inaccuracies and all the variables, but the issue is these devices are being used in populations. And can we provide guidance to the FDA and our colleagues or factors that they should consider about these uses, these devices being used in a CLIA-approved fashion, or would -- do they -- would they meet the definition or criteria that's currently utilized for CLIA approval? Or CLIA waivers, pardon me.

Dr. Cassiere.

DR. CASSIERE: Well, I could just speak for my health system, so when this all came down about off-label use, they did validation studies, and what they did is they took -- and, again, the ICU is a box, and there's a lot of things in the box, but they said, okay, if you're in the box, if you're in one of our ICUs, we're going to correlate finger stick glucoses with venous and arterial samples. And this is unpublished information; this is just internal. And they found very good correlation, which kind of justified us continuing to use the glucometers in the ICU.

But, with that said, once you open up the box and see how it's used, when is the glucometer used? That information, we don't know, but at least I can tell you from a health system point of view, we have 22 hospitals in our health system, so they just across the health system, very robust data, and our lab people felt very comfortable with the use of capillary glucose in the ICU population. But what they don't see is when we use the capillary blood glucose monitor, and I can tell you, just from working in a few of the intensive care units, it's on the patients that you would expect the capillary blood to be reliable.

What do I mean by that? They are normoxia, normal tensive, and they're recovering from their critical illness. It's not in the patient population who's hypothermic, on renal replacement therapy, mechanical assist devices, or that. So that's the guidance I think the

FDA needs, but it's really hard to pick, you know, what disease states it would be adverse to use in.

DR. ASTLES: So I'm going to open --

DR. BREMER: Dr. Astles. Thank you.

DR. ASTLES: This is Dr. Astles. I'm going to open up the Pandora's box about what is currently done and the CLIA problem of off-label use and them devolving to high complexity, which requires validation studies, possibly what you did, possibly requiring even more work. And then there's the difficulty of nurses doing testing, which they apparently are -- you know, would qualify under CLIA for the academic requirements, but then there's these additional requirements for work, experience in the laboratory, whatever that is interpreted to mean, and continuing a demonstration of proficiency or competency with the device, and so it's a complicated issue. I probably shouldn't have even brought it up before lunch, but there you are.

DR. BREMER: Yes. Dr. Cassiere.

Thank you.

DR. CASSIERE: I want to follow up on that. Dr. Tung had mentioned before, you know, whenever we get an abnormal value on these, the finger sticks, or even our venous and arterial sample, it's always validated. So if I have a patient who's on an insulin drip, they're at 10 units an hour and their finger stick the hour before was 220, and then the nurse approaches me and says the finger stick now is 400 or the finger stick now is 100, that's going to prompt a repeat test.

If it's a finger stick, it's going to prompt going to the stat blood gas lab and validating it, so buffered around the inaccuracies of the machine are repeat testing when the results are out of either range or don't make clinical sense, and that's important.

DR. BREMER: Dr. Lias. Thank you.

DR. LIAS: This is Courtney Lias. I do want to clarify that the question on CLIA is really surrounding the statutory requirements for CLIA, because there's the statutory language that we put up there. And we will have to determine whether or not, you know, if faced with the question, say we've cleared a meter for this use and we want to have the question, somebody wants waiver for it, we will have to provide information about why it meets that standard, so that is actually what we're looking for. I just wanted to clarify that.

DR. BREMER: Thank you.

DR. LIAS: If you believe it does or doesn't, or considerations that we should take into account when trying to determine whether it does or doesn't. But we will eventually, if faced with this question, have to document why we believe it does or doesn't meet that standard.

DR. BREMER: Thank you, Dr. Lias.

Dr. Grunberger.

DR. GRUNBERGER: Yes, and actually, those two last speakers I think really hit the target, because on one hand, Courtney, Dr. Lias, is stuck with the statutory language, and the simple, fine, we agree. It's the other one, the insignificant risk of erroneous result which obviously is the headache, but I think what Dr. Cassiere said is probably the best way to go about it.

The question is this is unpublished. Is there any way to publish your experience and go through peer review? And if so, you know, can that be sort of the basis for the future decision making? Because clearly, as you mentioned, you have a system, and I like the whole idea that the capillary sampling is reliable because you know on which patients to do it, and then so the question is would -- is that -- is there a plan to actually publish it so we can start that education process?

DR. CASSIERE: That's exactly what I asked my laboratory people and -- because I had

questioned them about the valuable information, and apparently, in order to use the -- and correct me if I'm wrong, in order to use these devices in the ICU, similar hospitals and health systems had to do this data collection to make sure they're not doing any untoward effects on the patients. So it's not just specific to my health system, and one of the other regulatory agents, the Department of Health came in from New York to look, to make sure that the data was sound, that if we're using our devices in the ICU. So the pushback from my pathology and laboratory people are, well, this wasn't data that was collected for a study; this is really data collected for regulatory reasons. And that doesn't mean it can't be published, but I could bring it back to my health system to see if that would be valuable.

DR. BREMER: Thank you.

Yes. Continue, please.

DR. CASSIERE: One last -- just to answer the question about the CLIA, so my understanding would be these devices meet the threshold for venous and arterial blood sampling. They do not meet the threshold for capillary blood sampling, so they can't get CLIA approved. So the next question is how do we bridge that for patients in the intensive care unit where we're not saying that it's still off label?

And that's where harm comes in, and that's where, I guess, we have to mitigate and leave it up to -- and, again, I'm going to say this again -- the bedside, the clinicians who are taking care of the patients to make the decision about whether an 85% or an 86% accuracy is going to do harm.

DR. BREMER: I'm going to ask Dr. Lias just to clarify our charge, and then Dr. Wyne.

DR. LIAS: This is Courtney Lias.

So all these pieces of feedback are helpful, and I'm really interested to hear, you know, the Panel's discussion on this point and the recommendations that you end up making. I do want to make sure that you understand the implications of what you just said

just so you make -- because CLIA is not -- and the reason that I'm making this clarification is because, you know, CLIA wouldn't be widely understood outside of the laboratory community.

So if we made the determination that the device was waived for arterial and venous blood but not waived for capillary blood, we can do that, and then that would mean that the high-complexity requirement -- I mean, the moderate-complexity maybe -- it would be different than high, but not much different practically -- the moderate-complexity requirements likely would apply to glucose meters at the point of care.

So, in some systems, that might be easier than high. In other systems, it may be very similar to high, so you know, that's a consideration to make.

DR. BREMER: I'd like Dr. Cassiere to finish up, and then Dr. Wyne.

DR. CASSIERE: Yeah, so just to follow up on that, is there a way of -- even though these studies -- again, all these studies and all that information we have is a black box. We don't know what's in the black box, so if you want to get CLIA clearance for capillary blood testing, why not mandate a validation study that I mentioned before? Because in my particular patients from the ICU, just because they're in the ICU, it'll be an off-label use, and it would be at a moderate complexity. But if that particular patient population, I had data to show that we met the threshold, can you still use the device with capillary sampling?

DR. LIAS: If the device were cleared for use but moderate complexity, you know, so if it were cleared, which is the two, you know, two questions that we have for input. If it were cleared and moderate complexity, it could be used at the bedside, but the laboratory overseeing the testing would have to meet moderate-complexity requirements, and no alterations could be made in moderate-complexity settings. Laboratories of high complexity could still use it off label and do high-complexity type things, but any user that wouldn't qualify under moderate-complexity requirements wouldn't be able to use it.

So the impact may be different than the high-complexity impact, and it probably varies a little across the institution about what the impact difference between moderate and waived testing would be. I will say that there are a lot of point of care devices that are moderate complexity. That's not unusual.

DR. BREMER: Thank you, Dr. Lias.

Dr. Wyne, then Ms. Lee.

DR. WYNE: So my question has to do, what population are we really talking about? I don't know what percent of glucose measurements in the ICU are actually done with capillary, and certainly a lot of the ones I see are done with arterial or venous. So it seems to me the issue is a little bit more using capillary outside the ICU, because again, if you've got devices that are only approved on arterial or venous, and you're frequently doing arterial or venous sticks in the ICU, probably the capillary's a small percentage of use, whereas outside the ICU, arterial or venous is probably a small percentage.

DR. LIAS: Courtney Lias.

So I don't know about now. In the last couple of years, it's possible that it has changed because of some of these things, to head more toward arterial and venous, but we certainly do have a lot of reports of capillary blood testing across the whole population. I will also anecdotally say when the Nova meter was cleared and waived for arterial and venous blood, there was a pretty big outcry about not getting capillary clearance for that population. And so, you know, obviously some people wanted to use it at that point, and the Nova meter, at least, is already cleared for capillary blood in other parts of the hospital and waived based on the data.

DR. BREMER: Thank you, Dr. Lias.

Ms. Lee.

DR. LEE: Rosemary Lee.

I just wanted to reinforce what Dr. Tung had mentioned earlier about the critical care guidelines. At the Society of Critical Care Medicine website, there are free downloadable guidelines, and the 2012 guidelines for use of insulin infusion in critical care, it asks when should alternatives to finger stick capillary sampling be used in adult ICU patients? And the response is "We suggest arterial or venous whole blood sampling instead of finger stick capillary blood glucose testing for patients in shock, on vasopressor therapy, or with severe peripheral edema, and for any patient on a prolonged insulin infusion." And the quality of evidence was considered moderate, so it kind of reinforces what we've been saying.

DR. BREMER: Thank you.

Dr. Cassiere.

DR. CASSIERE: So I'm just going to push back a little on those guidelines, you know, because you look at the data, the data's not perfect. And we have plenty of patients in our heart failure unit who have had LVADs, who have some edema that the finger sticks work out great. We would be precluding those patients, and some of those patients wind up in the ICU just for monitoring pump thrombosis, anticoagulation, things along that line. So, in my particular unit, probably 50% of the patients are monitored with finger sticks, so we do use a lot of finger sticks in our ICU.

And the other thing we didn't talk about is the IT interface with the glucose monitors. That is really helpful for us in terms of reviewing data, not that that should be something separate, but so I just wanted to bring up the -- even though those guidelines say what they say, again, in each individual subset of patients, there are going to be patient populations where capillary glucose monitoring can be used.

Using ABGs, an ABG machine to do glucose monitoring is about 1 to 3 cc, so in 24 hours you can really stack up blood per day as opposed to a finger stick. So, again, so this

taking blood from the artery in the vein can add up. Even though you can tell the nursing staff to take 0.5 or 1 cc, there's a lot of testing that we do on top of the point of care glucose thing. Lactates, ionized calcium, so there's a lot of other things that we're getting at the same time that -- so I wouldn't want to just pigeonhole that.

DR. BREMER: Thank you, Doctor.

Dr. Wyne.

DR. WYNE: But remember, when they're using the arterial blood, they're not getting 3 cc to run to a machine; they're getting as small as possible volume to put onto that device. So it's -- I mean, it's still a larger volume than if you were doing a finger stick, absolutely, but it's not as big a volume as if you're running a blood gas or running it over to a machine.

DR. BREMER: Dr. Cassiere.

DR. CASSIERE: So I observed our nursing staff and another of the units as well in my hospital, and I've never seen less than 1 cc of blood taken from a patient, even though they can take a small amount. A lot of it has to do -- how you have the circuit set up. Do you have a circuit where you have no waste or you have waste? It's very difficult, and most of the time they're -- it's almost always at least 1 cc.

DR. BREMER: Ms. Kirkpatrick.

MS. KIRKPATRICK: Sherry Kirkpatrick.

Just to build on that, in an arterial line, if you do have the closed circuit, we don't have waste, but implanted ports and central lines, there's always a minimum of 10 mL waste with our facility because of the flushing and -- so that would be really a problem for us.

DR. BREMER: Mr. Aviles.

HSCM AVILES: Mike Aviles.

I would just want to add on that as an end use, sometimes just the person trying to collect the sample always wants to err on the side of the more the better because you never know what you forgot or what the doctor will ask in the last minute, so just want to put that out there.

DR. BREMER: Thank you to the Panel for the discussion. Any other questions or comments? Again, this has been a -- I think what I'm hearing is that there's no quick answer, which is why we were all convened here to put our heads together, to try to provide some guidance, and I will push us to try to do -- to try to get as granular as we can, to fulfill our mission by the end of the day.

Next on the agenda is the Open Session, but before we transition, is there any comments from the Panel before we transition to the Open Session?

(No response.)

DR. BREMER: All right. Well, in that case we'll keep proceeding instead of -- instead of taking a 5-minute break now, we'll just, if okay with everyone, we'll proceed to the Open Session and maybe get you out a little bit early for lunch.

Okay, so back to the script, so we will now proceed with the Open Public Hearing portion of the meeting. Public attendees, we appreciate you being here, and are given the opportunity to address the Panel and to present data, information, or views relevant to the meeting agenda.

We will now read the Opening Public Hearing disclosure process statement, and I turn it over to Commander Garcia.

LCDR GARCIA: Thank you, Chair.

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 this 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 your meeting.

I turn it over back to you, Chair.

DR. BREMER: Thank you, Commander.

For the record, we have received -- this is for the transcriptionist -- nine formal requests to speak for today's meeting. Each scheduled speaker will be given 5 minutes to address the Panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting, and the Panel appreciates that each speaker remains cognizant of their speaking time.

Just for a point of operational procedures, what I'll do is I'll read the speaker as well as the next speaker. If you can throw something at me, raise your hand or something so I know you're here, that will help facilitate the flow, and then at the end, if there are those who have not registered, depending on time and availability, who wish to speak, we will recognize you as well.

So we will begin this session with Silka Clark from Aurora, Colorado, and next will be Jay Hupp from Tulsa, Oklahoma, and 5 minutes to speak each. Yes. Thank you.

MS. CLARK: I'm so excited to see my slides up here. Thank you for giving us this

opportunity to speak to this. It's been a hot topic for us for quite some time.

I am Silka Clark. Again, I am from Children's Hospital in Colorado, formerly the manager for the Centura Health Network in Colorado and Western Kansas. I've been a point of care coordinator for 12 years. I am obligated to say that Abbott Diabetes Care did pay for my travel and housing to be here but not my time.

I am a customer currently of both Abbott and Nova meters, and I'm here to advocate for clarification on next steps for use in validation of hospital-based glucose meters, specifically with regard to capillary testing in critically ill patients. I'm a stakeholder in choosing the technology that is used. I also design the training and competency assessment for nursing and all clinical staff that use the meter. It's not just nurses. And I am someone who does the validation studies for those devices as well.

And I decided to present to you a study that I did, actually right after this came out in 2014. I'm going to kind of skip the whole slide on the background because you guys covered that really well for us, but it was panic in our department when we heard that this little word, "critically ill," in this package insert suddenly meant that we were using our meters off label that we had been using for the past 5 to maybe much longer years and never really thought about that. Not using them in the ICUs was not an option.

So what I quickly did was put together a study, retroactive study of our testing specific to ICU. I deleted any data point where a lab test was not done within 5 minutes, so I was little bit more strict with my timeline. We do approximately 750,000 glucose tests per year in our system, and so that was a significant number, but out of all of those, 459 were done within 5 minutes of each other, usually when they send a comp metabolic or basic to the lab at the same time as a finger stick in the morning.

And you can see here our data looked really good below 75. It's not terribly tough to meet that requirement, to be within +/- 12 mg/dL under 75. It's when you get much wider,

higher in the range that it gets a little harder. I think a question was asked about how many are outliers, and for us, 50% of the outliers that were more than 15% were above 180 mg/dL, so I don't know if that matters.

Correlation was great for us, so we had to move on, and we put this in front of our medical board. We also did a little bit of a sensitivity/specificity study with regard to hypo and hyperglycemia within our system. We wanted to know is it accurate? Even if it's not meeting these tighter FDA guidelines, is it accurate for hypo and hyperglycemia based on the ranges that we were using in our ICUs? And we found that it was accurate. We saw 96% to 97% accuracy in that population. In our newborn nursery, that was at 93%.

I did present this as a poster to AACC in 2015 and focusing on that sensitivity and specificity for hypo and hyperglycemia.

By far the most difficult task was defining critically ill. We decided that it was all patients in ICU or NICU. As a point of care coordinator, to chase down results when you're looking at 750,000 data points per year and trying to audit whether or not they followed protocol for each individual test was much harder than monitoring a subset of glucometers and calling them high-complexity analyzers and training those end-users as high-complexity testing staff, so that is the approach that we took.

The nurses in those departments were then considered high-complexity testing personnel. We did have to go back and review transcripts, so for about 2,000 different nurses in our system of 17 hospitals, we had to review diploma transcripts to make sure that they qualified to perform those, because a CNA is different than an RN, and CNAs tend to do the majority of the glucose tests, so we actually had to eliminate them as users in the ICU and only the RNs could do the testing.

And then we also had to treat each meter as a high-complexity analyzer, so it had to have a 6-month linearity method comparison, participate in proficiency testing. All test

operators also had to have a 6-month competency assessment and annual competency assessment for all six elements of competency by CLIA, which was different than the waived test.

My time is up. Thank you.

DR. BREMER: Thank you.

Next, we will hear from Jay Hupp from Tulsa, California [sic], followed by Helena Duncan from Washington, D.C.

MR. HUPP: Good morning. My name is Jay Hupp, and I'm a lab technical services manager at St. Francis Health System in Tulsa, Oklahoma. I have been selected by Abbott to present this information on their behalf.

I'd like to cover four main topics here, the first being rapid glucose results by glucometer; next, glucometer use on critically ill patients; limitations and indications for use; and also laboratory results and clinical judgment.

Glucose results obtained by capillary specimen via glucometer, any vendor, plays an important role in the management of patients across all clinical areas of the hospital. The majority of glucoses performed via glucometer are done on capillary specimens. Capillary specimens are easy to obtain. They provide rapid results to clinicians. Arterial, venous, and line draws are more invasive, require more testing supplies and involve more labor, and results are not as readily available.

Testing performed on a glucometer is more cost effective than glucose performed on a blood gas analyzer or on any other patient point of care testing device. Rapid results mean decisions can be made quickly for the vast majority of patients, which improves their quality of care and their outcomes.

Sending specimens to the central lab for all glucose determinations is costly, much more time would be involved, and it would be a burden to most already short-staffed

laboratories.

Glucometers are used on a large scale, and maintaining the waived status makes the device much more easy to manage. Additionally, waived status allows for certified personnel, including nursing, to use their education and skills to care for patients.

Next, glucometer use on critically ill patients: Patients can transition from stable to critically ill whether or not they're in a critical care area. I know I've heard of institutions that have defined critically ill as only patients in a code blue situation. Others have defined it as only patients in a critical care area. And still others have defined it as emergency room patients. Limiting glucometer usage to only non-critical patients is problematic and inconsistent since each institution can establish their own definition.

Limitations and indications for use: Limitations and indications for use should be followed not just for the glucometer but for all assays performed at the point of care and the central lab. These two parts of a package insert are often the first sections read by laboratorians and play an important role in the overall evaluation of a test. This review process has been good laboratory practice for years, even before critically ill and glucometers became an issue. Education regarding limitations and indications for use is typically done through initial training and competency assessment.

And, lastly, laboratory results and clinical judgment: Physicians, nurses, and personnel responsible for patient care should correlate test results with clinical findings. It doesn't matter whether it is a glucometer result or a result from a comprehensive metabolic panel. Nursing and physicians should evaluate all test results in the context of the patient.

Thank you for your time.

DR. BREMER: Thank you for your comments.

Now we'll hear from Helena Duncan from Washington, D.C., followed by Gary

Scheiner from Wynnewood, Pennsylvania.

MS. DUNCAN: Good morning. My name is Helena Duncan, and I am here today representing the College of American Pathologists.

The CAP appreciates this opportunity to provide our perspective regarding blood cancer measurement using capillary blood with blood glucose meters in all hospital patients, including those receiving intensive medical intervention therapy and patients with decreased peripheral blood flow, such as hypertension, shock, and other patients in intensive care settings.

As the world's largest organization of board-certified pathologists and leading providers of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in patients with pathology and laboratory medicine worldwide.

Control of blood glucose in an acceptable range remains a goal for diabetes patients in both hospital and outpatient environments. It is necessary to monitor blood glucose levels often with bedside glucose meters in these patients, so the appropriate types and quantities of medication and food can be delivered to them in a timely manner. The ease of using these devices and rapid reporting of blood glucose information lead to their utilization in inpatient settings for diabetic and non-diabetic patients, and established as a standard of care.

Therefore, the CAP supports using capillary blood with blood glucose meters for critically ill patient populations provided the manufacturer's clinical data validates performance in each patient population. There are numerous studies, clinical studies such as guidelines from the Clinical Laboratory Standards Institute on blood glucose meter performance expectations. However, we do believe there may be specific limitations cited in the literature in which the meters should not be used for capillary samples, including and

among others severe hypotension, dehydration, and shock.

In conclusion, the CAP supports the use of capillary blood with blood glucose meters for patient populations in hospitals provided the manufacturers' clinical data validates performance in each intended population, patient population.

Thank you for your consideration of these comments.

DR. BREMER: Thank you for your comments.

Now we'll hear from Gary Scheiner from Wynnewood, Pennsylvania, followed by Angela Garner. Is Ms. Garner in the room? Thank you, and following Ms. Garner will be Deanna Bogner.

MS. GARNER: Good morning. My name is Angela Garner. Abbott Diabetes Care paid for my travel and housing to be here today but not my time. I've been looking forward to being here today, so thank you for allowing me the opportunity to speak.

I am currently the supervisor of point of care testing for MultiCare Health System located in Tacoma, Washington. We have approximately 6,000 staff that performs glucose testing, using -- we have a little over 500 glucometers throughout the system, all of which are interfaced to our electronic medical record.

As a laboratory professional for the last 28 years, the last 10 years in point of care specifically, I can share with you that glucose meters are the most common, most requested, most preformed, and most billed for point of care test over all other tests that we do at the point of care. This, to me, speaks volumes on how critical these results are to clinicians who are making treatment decisions for those that are seeking medical care.

I would like to shift to discuss the ideas around using or not using a glucose meter on critically ill patients and, most importantly, the impacts to patient care outcomes.

The first challenge was to try and determine a definition for critically ill. We were given very little guidance on what this truly meant. The definition varies across the board,

and there is not an acceptable, universal definition. It is possible that if you go into different units, different facilities, different specialties or subspecialties, different organizations, etc., their definition of critically ill will be different because they treat different patients with different medical issues, which could be considered critically ill in their specialty or subspecialty.

CLSI document POCT17, Use of Glucose Meters for Critically Ill Patients, has been helpful in sorting some options to define critically ill. I found the most logical way for our healthcare system to define critically ill and minimize impact to patients and clinicians was to take the limitations in the package insert and use those as the definition for critically ill. These limitations were already part of policy and procedure, training and competency assessment programs, and therefore processes already being met and in place.

Sorry. Let me just get down here.

Not being able to use the glucose meter on critically ill patients via capillary sample certainly has some tradeoffs. I think it is a fair question to ask if these tradeoffs are what are best for patient outcomes. Are we considering all aspects of what is best for patients and their care, or are we creating additional patient care issues by not allowing for glucose testing via a glucose meter using a capillary sample? A glucose meter can give a clinician a glucose result in a matter of seconds using a capillary sample. This allows that clinician to use that result, along with other clinical information, to make a rapid determination of a treatment plan.

Sending a sample to the laboratory, stat even, we are looking at least a 30-minute turnaround time, and that's if you have a good lab that has a great turnaround time. Even the turnaround time from the lab can vary depending on the laboratory that you're working with. What kind of implications does this mean for the critically ill patient, and what are the ramifications to patient outcomes that this huge difference in time contributes to?

It's not easy to move your slides when your hand's shaking a little, so I apologize.

For the sample to be sent to the lab, it requires a venipuncture procedure to be performed. Why is this a concern? Well, one reason is because venipuncture requires a larger volume of blood than a capillary sample. For patients that are critically ill, we should be trying to minimize the sample volume. These patients also at times are difficult draws to perform venipuncture on. In those cases, we are potentially looking at a longer delay in getting results for the clinicians to act on. There could be further complications and concerns if these need to be serial drawn. Being able to perform the glucose testing on the glucose meter using a capillary sample on a critically ill patient removes these challenges.

It is important to also share that in some states, my state being one of them, the ability to perform venipuncture requires special credentialing if it is considered an outside position, the scope of practice.

In closing, the benefits of using a glucose meter should not be underestimated with regard to the value it brings to assisting in positive patient outcomes. They provide fast results, quick turnaround time, and this piece of the puzzle is important for those clinicians to have immediately.

Thank you.

DR. BREMER: Thank you for your comments.

Next we will hear from Deanna Bogner followed by Stephanie Fox-Rawlings from Washington, D.C.

MS. BOGNER: My name is Deanna Bogner, and I am a point of care testing coordinator from San Antonio, Texas. I have gone through progressively larger healthcare systems in my 20-plus years of managing point of care. I estimate that I have supervised 12 million glucose tests and trained over 25,000 operators. I have paid for this trip out of my pocket, using my own vacation, with no slides. I just have my opinions and experiences.

While you're listening to me speak in this presentation, please keep a dining room chair in mind. The dining room chair has four legs. The seat fails if any of those four legs fail. I will assign each of these legs to a label pertaining to the issue in front of the Committee: glucose meters, capillary sampling, and the ludicrous phrase of critical patient.

The first leg of the chair is the current glucose meter vendors. I have some recommendations for the Committee. The critical patient caveat should be eliminated from the lexicon of glucose meters, especially package inserts. The phrase was ill considered and functionally invalid due to the different definitions through each hospital and the fact that this Committee has already made the point that patients change over time, so it's going to be very difficult to figure out exactly who we need to point this high-complexity device at.

While we all want the best for the patient, accuracy is not the only piece of the puzzle that we have to use to pick a glucose meter. There are some pieces, like the IT piece, the middleware piece, and other things such as the back-end operating cost of the meter, that are going to be very much as important as the accuracy. The other thing is, is we've already used these meters in a whole hospital environment for 20 years.

The second piece of this chair is the point of care testing coordinator. Point of care did not exist as a laboratory discipline 20 years ago. When I got it, they said, oh, must be nice to be sitting in your office for all these times just making phone calls, not understanding that I supervised 500 tests a -- 500,000 a year. Point of care, CLIA, and the deemed status organizations tell me I must train all operators. I must train them for how to use the meter, how to do a finger stick, and any other thing that I -- who -- I do the curriculum, consider valid, and this includes places and situations where the meter is precluded from being used.

This is required to be enforced every year through competencies. It also identifies teaching and coaching opportunities and tells you -- tells me who may, through the

software, not be allowed to use the meter.

The third leg of the chair applies to the patient care personnel who use this tool. Consider how your car has evolved in the last 20 years. You still use it to get from place to place, right? Right now, it's just got back backup cameras and a whole lot more air bags. Glucose meters have evolved along with the patient care personnel that have used them, but they still use them in the same manner, with the same critical thinking skills, with the same education from the point of care person, with the knowledge of their patient, with the drugs administered. And under the direction of a physician, they are -- any comorbidities that can impact this, those are noted and under some pretty strict laboratory guidelines from the deemed status organizations. They use it with handoff communication to a licensed provider. This is required from over and above the laboratory. In all hospitals, the operators use the clinical laboratory as their reference.

As an evolution of glucose meters have progressed, from whole blood strips to the color charts to the current blood systems available, the fourth leg of the chair is new technology. The FDA has approved at least two continuous monitoring systems that I am aware of and has discussed new technology yesterday. This isn't available for the hospital yet, but it's coming.

In conclusion, glucose meters probably aren't going to be removed from the hospital environment any time soon in the United States. Glucose meters allow patients to be cared for using the waived designation and capillary sample, using critical thinking skills, established protocols, and education. I urge the Committee to remove the critical patient phrase from all package inserts and to allow the waived designation to stay in place.

Thank you for your time and attention.

One more comment. I have 12 seconds. If you change these glucose meters to moderately complex -- I have three operators -- that requires a demonstration every

6 months for every operator because my people jump around like grasshoppers. Okay. Just let's say that.

Thank you for your time and your attention.

DR. BREMER: Thank you for your comments.

Now we hear, if she's in the room, Dr. Stephanie Fox-Rawlings. I did not see a hand before, but -- okay. Then next we will hear from Robert DeCresce, Dr. Robert Decresce, followed by Jamie Petterson. Or maybe not. Is Dr. DeCresce in the room? How about Jamie Petterson? We did have one add-on, and then Dr. David Klonoff is -- I'll invite Dr. Klonoff to the podium, and then we will move into -- if there's others in the audience that would like to participate, we do have time.

Dr. Klonoff.

DR. KLONOFF: Hello. Thank you for allowing me to speak to this group. I'm David Klonoff, Medical Director of the Diabetes Research Institute at Mills Peninsula Medical Center in San Mateo.

I think this is a really important issue, and I think the group is actually ready to make a decision today. I would like to provide some information about where we've been to get to this point and then talk about what we can do at this point.

Back in early 2014, after CMS recognized that there might be a problem with the use of point of care blood glucose monitors in critically ill patients, I chaired a meeting here in Washington, D.C., among experts in diabetes and clinical chemistry to look at whether this policy of CMS to issue citations to hospitals using this practice was reasonable. The consensus was that it was not reasonable, and a group of us ended up writing an article, first in the October 2014 issue of *Mayo Clinic Proceedings*, called "Timely Hospital Glucose Measurement: Here Today, Gone Tomorrow." And then a year later a group of us, through the PRIDE organization of endos, wrote an article which was a statement in -- this in *JCE&M,*

October 2015, about the need for a moratorium.

And, in fact, it appears that there was a moratorium, but the reasons we gave for a moratorium were that although there were perhaps problems with blood glucose monitoring that had been pointed out through various investigators we've heard about, that there weren't necessarily good alternatives. So what we needed was better information about how good or how bad is blood glucose monitoring at the bedside and how good or how bad are the alternatives.

We've heard some comments about the alternatives. I would just like to repeat some of them once more because I don't think we should be in a situation where we say perfect is the enemy of good. If we -- to the extent that we're criticizing use of blood glucose monitoring, then we have to have to something better. We can't just throw everything out. So we've already heard that if you send a specimen to the lab, you're going to lose accuracy. The glucose level has been shown to fall by 5% to 7% in 2 hours. Plus you don't get timely treatment, which is a big problem. The glucose level itself can change in the patient.

Another alternative, which CMS recommended, was using blood gas analyzers. Last year in *Mayo Clinic Proceedings*, I and a group from Vanderbilt reported the largest study of the accuracy of blood glucose analyzers from the Vanderbilt lab, and guess what? Those analyzers did not meet FDA standards as of 2014 or 2016. So if we're going to move people off of glucose monitoring, we've got to move them onto something that presumably is accurate. I would say that that study we did showed that blood glucose analyzers are not necessarily accurate, not to mention the blood loss problem we heard about, and they also require a lot of maintenance, which is an added cost for the hospitals.

And if we talk about, well, let's just make this high complexity, now you've got other issues to deal with, such as the validation issue, record keeping, licensing of staff. In some

states, registered nurses aren't even allowed to do the study, so now you have to hire technicians. And I'll tell you, there is a shortage of technicians, so we can't even say just hire technicians. You can't create technicians that don't exist.

So where are we? The last factor that we talked about in our papers was let's get some data as to how accurate the glucose monitors are. Well, today, for the first time, I've seen this data. I wish it was, you know, world class and everything, but when I study this, what I've noticed is that the readings that are 75 and above are actually pretty good. Those meet the FDA required guidelines. Under 75 doesn't.

So my recommendation would be that we already know from those two studies, which we've heard are probably representative of all glucose monitors in hospital patients. My recommendation would be that we accept those readings for glucose levels 75 and above. The manufacturers have demonstrated that they're adequately accurate.

For readings under 75, I would suggest we say for those, we can't accept it, and we have to send a confirmatory lab test. Fortunately, most results are over 75, so it wouldn't be a total burden on the hospital, but I think that's a compromise which fits the accuracy and offers protection for the risk of hypoglycemia.

So we're talking about is this a high-risk procedure? I would submit that if we're looking at 75 or more and the numbers fit the FDA requirements, I would not call it high risk. If it's under 75, it has to be treated differently.

Thank you very much.

DR. BREMER: Thank you for your comments.

Again, in the sake of time, we do have time. If there is anyone else in the audience that would like to come to the microphone and give a -- and make a statement. We will adhere to the 5-minute rule just in the spirit of fairness, but please come up, and for the record, for the transcription, please, your name and affiliation. Thank you.

MR. PRICE: Sure. My name is David Price. I'm Vice President of Medical Affairs at Dexcom, but I'm not speaking on behalf of Dexcom. I'm speaking in part of what I did in my prior career at one of the blood glucose monitoring companies.

And I just wanted to raise a question and a point, and that's in the studies that were presented on the different glucose meters, were the comparisons being obtained from the same matrix? So was the meter compared to a laboratory reference obtained with venous, or was it obtained from capillary? Because if it's obtained from venous and the meter is being measured on capillary, there are matrix differences in glucoses. And we, in fact, demonstrated that with YSI in my past life, in which glucoses were obtained from a reference instrument venous and a reference instrument in capillaries, and they were in really good agreement at steady state glucose, but when glucoses were rapidly changing, there was a little difference between capillary -- there was difference between capillary and venous reference glucose.

DR. BREMER: Thank you, and during course of this, this is an opportunity for statements rather than discourse with the Panel or questions, but your -- I think your point is well taken and appreciated. Thank you.

Is there anyone else in the audience that would like to make a statement to our group to consider? Please.

(Off microphone comments.)

DR. BREMER: I was just told it's my discretion. I never hear that. I think we have time, and I think if it's pertinent to the conversation and relevant, please come up.

MS. GARNER: I'm Angela Garner. Again, I was -- my travel and lodging were paid for by Abbott Diabetes Care, but I just wanted to briefly discuss the moderate complexity that was brought up.

That is a huge game changer for healthcare systems. Going from waived to

moderate is going to have a huge impact. It goes from -- and, you know, initial training and annual competency, to initial training, 6-month competency, a 12-month competency, annual competencies thereafter, and then participation in proficiency testing, so this looks very different than waived, and I just wanted to share that, that it's not as simple as it may sound.

Thank you.

DR. BREMER: Thank you, and I appreciate that point. I think we do recognize that.

I do also want to engage our Panel. We have people in the audience with expertise and experience. Are there any questions from the Panel for anyone that -- yes.

Dr. Lias.

DR. LIAS: I have two comments for the Panel to consider.

DR. BREMER: Please.

DR. LIAS: We just heard a commenter mention that the data presented on capillary blood above 75 meets some certain criteria. I do want to clarify, it doesn't meet any of the criteria that are out there, either FDA's guidance documents or any other ones, so both below and 75 don't meet those criteria, any of them.

And then the second clarification I would have the Panel consider is it is true that there is a difference between capillary and venous blood, and that's definitely something we'd like to hear and put on, if the Panel wants to discuss that. I would also consider, though, that the difference between the capillary and venous blood was more pronounced in the intensive care population than the healthy population.

DR. BREMER: Thank you, Dr. Lias.

Again, we have -- we are blessed with a little time. If there are questions --

Yes, Ms. Petersen.

MS. PETERSEN: I don't have a question, but I'm wondering if there's another

comment period for the Panel or -- I'm a little confused because it looks like the agenda's changing and I'm not on the same page.

DR. BREMER: Oh, no worries. This is an opportunity that we, that the Panel has to ask anyone who just made a comment or came to the podium from the Open Public Session if you want clarification or a question.

(No response.)

DR. BREMER: So we are now at 11:30. If there's no other conversations or questions right now, we will go ahead and have a little bit longer lunch break. Per our guidelines and per the program, we will reconvene at 1 p.m., and that is for another Public Hearing, to be fair to those who had planned to be here at 1 o'clock.

Some housekeeping rules for lunch. Committee members, please do think about the questions that have been posed to us. They're not easy, and I ask you to think about creative ways and ways that we can be useful and informative to the FDA and our other colleagues. That said, please do not discuss the meeting topic during lunch amongst yourselves or with any other member of the audience. This is for personal reflection during lunch.

We will reconvene in this room at 1 o'clock, which is about an hour and a half from now. I will ask that all Committee members please return on time so we can be fair to those who come in at 1 for the second Public Hearing.

Audience members, please remember to take all of your personal belongings with you at this point in time. This room will be vacated during the lunch hour and a half. There will be FDA staff here, but please, all personal belongings should be taken with you at this point.

Commander Garcia, did I forget anything?

CDR GARCIA: We're good.

DR. BREMER: Okay. Thank you, everyone. I look forward to resuming the conversations at 1 p.m. Have a good lunch.

(Whereupon, at 11:30 a.m., a lunch recess was taken.)

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

(1:02 p.m.)

DR. BREMER: Okay. Thank you to everyone. For the record and for the transcriptionist, it is now 2 after 1, and we'll go ahead and resume this meeting.

In efforts to accommodate the public and those who have traveled and journeyed to impart their comments, I would like to resume the meeting with a Open Public Hearing segment. Again, we do appreciate those who have traveled and appreciate input, so I know we had an open session prior to lunch, but some may not have been here, so I do want to open it up to the audience.

If there is anyone who would like to make a public comment, in the spirit of being equitable, I will ask that it be limited to 5 minutes, but the podium is open, and I would ask that you state your name and affiliation for the public record before speaking.

Is there anyone in the audience that was either not here this morning or that would like to make a public statement for the Panel?

(No response.)

DR. BREMER: Going once.

(No response.)

DR. BREMER: Wonderful. No, you are not obligated, but I want to make sure that everyone has the opportunity. Seeing no one from the public that wants to make any additional comments that weren't already made, I want to again reiterate my thanks to you for being here and for your participation.

With that, we will move to our task at hand and go back to my script here. Okay, so what we have before us now are the questions posed to us by the FDA, and so let me read this, and then I'm going to ask for some points of clarification before we start our next round of discussions at the table.

So at this time we will focus our discussion as a Panel on the FDA questions presented to us by Dr. Lias. Copies of the questions are in your panel folders. I want to remind the Panel that this is a deliberation period amongst the Panel members only, and our task at hand is to answer, in as granular a fashion, the FDA questions based on the data in the panel packs, the presentations, and the expertise around the table, and you all have been selected because you bring to the table expertise that we very much appreciate.

With this said, just for the public record, I will try to identify hands as they go up, but if I don't state your name, please do announce your name before giving comment.

And, as Chair, I'm going to kind of summarize where I feel the discussion should -- could potentially go from here, although I leave it to my colleagues to generate the discourse. The issues that I kind of see that have come up this morning are kind of twofold, which pertain to the questions: One is really with the issues regarding use and assessment of blood glucose meters in the hospitalized setting in the intensive setting, and risks and benefits and some of the caveats that we discussed about the use and assessment of the device. A very separate issue is the issue of the CLIA question regarding the moderate labeling versus a waiver. And I'm going to tap into the expertise of our Panel, if you don't mind, and ask Dr. Astles to kind of just make sure we're all on the same page on some of the implications regarding a waiver versus a moderate indication for CLIA.

Dr. Astles. Thank you.

DR. ASTLES: Thank you, and I'm going to ask my colleague from CMS, Dara Lynn (ph.), to back me up and correct me if I do stray, and I might.

Any of the three categorizations require some determination. Now, that's done by FDA, and obviously a waived test should be accurate, pose no -- let me just read it -- "pose no reasonable risk of harm to the patient if the test is performed incorrectly, employ methodologies that are so simple and accurate as to render the likelihood of erroneous

results negligible, or are cleared by FDA for home use." So those are "ors"; those are not "ands." So the last one in particular may be relevant, "pose no reasonable risk of harm to the patient if the test is performed incorrectly."

But your question is really about how waived testing is performed and what the quality controls are and so forth. And I'll just say the succinct answer is once a test is waived through any mechanism, it can be used by -- it can be used in a CLIA-certified laboratory that is certified for waiver, but all bets are sort of off. The user should have and use the product insert and follow it, but work we've done, CMS has done to inspect laboratories on a spot basis, a sampling, shows that that doesn't always happen.

In essence, a waived test need not have any quality control done, no proficiency testing. There are no special requirements at all for personnel, other than that they, you know, they work in a waived setting, and that's true for all waived tests. It gets a little more gray when we talk about how waived tests are used in laboratories that are CAP accredited, for example, in those settings, and we've heard speakers who are point of care coordinators in settings like that. It's likely that the accreditation organization does require something -- you know, they're not going to let it be wide open.

So there may -- it may be that in many institutions that treat critically ill patients, waived tests do get more attention, and there is some quality control and things done to monitor performance. We've not talked really about settings like ambulances and others where critically ill patients might be tested with glucose meters and if in those settings, if -- you know, if we're talking about waiving use that is currently not waivable, it's difficult for me to know what kinds of quality control, what kind of attention and all of this, the discussions we've talked about, might depend upon some kind of education. That's been brought up quite a bit, you know, educating the public about the problems with capillary testing in these patients. So it's a little more complicated when we're thinking about if

we're going to allow that in waived settings, how do you get to all of these various -- because it's, you know, it's nursing homes, perhaps home health testing, and I can't remember exactly, maybe Dara Lynn remembers, but waived testing is done in something like 150,000 -- what is the number? Is it close to that? -- 150,000 settings, probably most of them do glucose testing. What's the fraction of those that might be testing patients that are, you know, critical? That's not clear to me, but is there any direct questions I can answer about it?

DR. BREMER: No, and I appreciate the input. The reason I asked is I think that's one of the questions that they ask, that the FDA is asking for guidance on, and that it's -- I don't think it's a clear-cut decision, and I think that's why we want the expertise.

And Dr. Lias for clarification.

DR. LIAS: Yeah. I would agree with that, and I would add, I think, some of the main differences as were mentioned is the waived labs don't require proficiency testing, and moderate-complexity labs do require proficiency testing. The personnel requirements, testing personnel for moderate complexity require at least a high school degree, and there is no requirements for who does the testing in waived labs. And then there's a biennial assessment of the quality -- I mean, there's a biennial inspection by CMS on those devices for moderate complexity and very little inspection by CMS for waived testing.

And then what's the other one? Quality, you have to have a quality control and quality assessment program for moderates, but for waived testing you only have to follow the instructions. It's not part of a -- as was mentioned too, though, some hospitals treat some of those aspects for their meters just like some of their other tests.

DR. BREMER: Thank you, Dr. Lias.

Dr. Cassiere.

DR. CASSIERE: So this may sound like a naive question, but just like all II class

devices are not -- all Class II, some of them have special requirements in terms of following. Is there such a thing as a CLIA waiver with special requirements? And is that something that can help us get out of this box?

DR. BREMER: I would have to defer to Dr. Lias.

DR. LIAS: No.

(Laughter.)

DR. ASTLES: I'll just add that the only time I ever saw that happen was with HIV testing, and then I think FDA did request, require some training.

DR. LIAS: So but I think there the issue is that waived laboratories must follow the instructions for use or it's not waived. Then you get into that off-label scenario. So as soon as you don't follow the instructions for use, you're in the off-label realm, and so if the label says some instructions for doing something, that is what the waived lab must do. That would be part of the clearance decision, not part of the waiver decision.

DR. ASTLES: Yeah. The difficulty is that once it's in a waived setting, no one will know that it's not being used -- that it's being used off label. It will just simply never be caught.

DR. BREMER: Thank you for the clarification.

Yes, Dr. -- and I wanted -- Dr. Lakos, you're next, but I think this is -- we're getting into the weeds, which I appreciate because this is a difficult question and this is why we're here.

Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

I just would like to add some information, which is publicly available, and just to add to the complexity of the question, which I think goes beyond glucose. The Centers for Medicare and Medicaid Services recently published a memo where they weighed in, saying

that a nursing degree is a science degree, making nurses qualified to perform non-waived tests. So, obviously, this is just a recommendation, and I don't think this is the way to go, and I -- in fact, a couple of professional organizations like AACC's position against it, but it's all about this point of care that's the discussion, so it's really creating a lot of controversy out there.

DR. BREMER: Thank you. Okay, so we'll proceed -- oh, yes, I'm sorry.

Ms. Petersen.

MS. PETERSEN: Thank you. Carolyn Petersen.

So in listening to all of this discussion today, you know, I come more from the consumer perspective, and I'm not going to try to talk about the technical aspects of the things that you all do every day. But what's really struck me is that while the questions are framed in a particular way, looking at this capillary blood glucose determination and when this is appropriate in inpatient settings, I think we really have two issues going on here.

We have first this issue about a particular technology in a particular setting, but we also have the broader patient experience, and that includes things like outcomes. This morning Dr. Cassiere had talked about the need for the clinician to be involved in assessing what tests are appropriate and what kinds of information you really need in making a determination.

Ms. McCollister-Slipp and others had talked about the variation in patients, even among people who have the same diagnosis or perhaps some similarities about their particular characteristics. I think that's also something that needs to be explored in terms of getting FDA information that it can use to further the pathway about when we can use this technology and what's appropriate.

We need to bear in mind that just because we can measure something doesn't mean that we should measure something. Or that we should measure it in a particular way.

This morning a suggestion was made that as the technology progresses, we should be looking at the continuous glucose monitoring for patients, because that's something we can now do, and advanced practice nurses, nurses in the ICU are able to manage all these various technologies.

Certainly, some patients really would benefit from that, but there are others who might find this to be yet another stressor on top of all the other stressors that they experience in the hospital: the noise, the lights, the lack of privacy, the significant changes from personal routines. And so there's value in thinking about how do we identify the patients who can really benefit from which types of measurements, and where are we able to tolerate a little bit more variation, given a diagnosis, a person's outcome, age, and so forth.

And so I think, in the spirit of trying to help FDA get a better handle on when they are wanting to use these capillary blood glucose measurements, we can be thinking about how to help them explore things that encourage the use of data from different sets with different devices so that we can get some development of algorithms that help to pinpoint when it's appropriate or when one is more likely to get a particular outcome that clinicians can use in making their decisions and people who are continuously working with the patients in the units can use as a reference in terms of determining when they bring in a clinician to make a breakpoint decision.

We also can look at accumulating data, and perhaps interactions with PCORI or with NIH or others who can help move the science forward, so that clinicians, panels such as this one, FDA, and others are able to work together on coming up with some more appropriate guidelines that get at the questions we're looking at today. You know, FDA is really not an organization that's in the business of gathering evidence or creating guidelines or building standards, but certainly, it has a role to work with organizations and agencies that do those

things. Perhaps if we can help them identify a pathway in that direction, we can get to better identifying patients who will benefit most from different opportunities with these devices for blood glucose management and thereby get the right treatment to the right patient at the right time.

Thank you.

DR. BREMER: Thank you.

Dr. Tung.

DR. TUNG: I was going to say, as a clinician, I participate in proficiency testing for what my hospital interprets as a moderate-complexity monitor, which is blood gas measurement, and so twice a year I have to show that I can measure a blood gas and extract a number out of the machine. It's actually useful because there are some subtleties in the measurement you wouldn't otherwise know unless you did it and someone who knew what was doing told you what to do.

So I imagine that whatever 85% effectiveness that currently exists is going to go down if you waive because there will be less regulation of how people do it. I think you have to predict that.

DR. BREMER: Okay, so operationally, what I -- if the Panel will entertain it, I will -- we have the question in front of us. I'll go ahead and read the top lines, but not -- oh, I'm sorry.

Dr. Nipper.

DR. NIPPER: I was thinking about one of the public comments who kindly gave us some Bayesian statistics to look at, about the fact that we really don't have good data as far as sensitivity, specificity, predictive value of a positive or negative result on patients who are critically ill in the ICU with these devices.

So if the indication is that we need to do a capillary glucose on someone who is

critically ill, we need to know what the sensitivity of that measurement is and what the indications for it are, and then, once we can -- if we can document the indication and then see how well it does in identifying the clinical -- or missing a clinical setting, as Dr. Hugh has said so eloquently, then maybe we can know where a cutoff or a stop line would be in using capillary blood for a sample and we know when to go to arterial or venous.

We don't have that data, and yet we were tickled with that by one of the public commenters whose name I'm sorry I've failed to record. There was some data in there, and I don't know how much more we need, etc., but I think clinical evidence-based decision making is called for here, and we need to have that in order to know what the indication for the test is if we're doing, in fact, capillary glucose in the ICU.

DR. BREMER: Thank you for the comment, and that comment did come from Silka Clark, I believe was who presented that to the --

Thank you, Silka. Okay. Thank you.

Yes, and Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: I'm still trying to wrap my head around the fact what exactly is the risk that we're trying to mitigate here, and what is the concern? I mean, it's pretty obvious to me, I think it has been for quite some time, that we don't have a lot of data that I think is particularly reflective of real-world use, whether that be an outpatient setting or whether that be in the inpatient setting, although to be honest that's something I haven't thought that much about until, you know, in advance of this setting, when it comes to capillary blood glucose levels.

So, I mean, as a patient, the idea of somebody -- of being unconscious and having a clinician dose me based off of capillary blood tests when I'm in sepsis, which I've been in a couple of times, unconscious or, you know, the ER or whatever, with DKA, makes me really nervous just because there's -- it just -- that makes me really nervous to think about. On

the other hand, I don't -- I'm a big believer in not letting the perfect be the enemy of the good, so we don't want to create other issues by trying to mitigate that risk, which may be a de minimis risk in, you know, 90% of the cases.

So what is it we're trying to prevent here? Just errors based on dosing with nonaccurate information?

DR. LIAS: I'll let the -- this is Courtney Lias. I'll let the clinicians weigh in on other risks. I do know that adverse event reports include things like inaccurate dosing because of inaccurate glucose values in the hospital setting. Other adverse events including missing hypoglycemia or hyperglycemia because of inaccurate glucose values, so that's the general categories of adverse events that are reported to FDA, but I'll let others weigh in on what the biggest concerns might be, or smallest.

DR. BREMER: Dr. Cassiere.

DR. CASSIERE: Yeah, so great question. So there was a subanalysis done of the NICE-SUGAR trial in *New England Journal of Medicine*, and what they did is they broke down moderate hypoglycemia and severe hypoglycemia. Severe was a glucose less than 40. Moderate was 41 to I believe it was 70, and the patients who developed severe hypoglycemia doubled their mortality rate. Patients who had moderate hypoglycemia, their mortality went up between 40% and 50%.

So I think that's one of the fears. That study was -- their tight glucose control was 80 to 110, I believe, or 100, which is really tight, so that's the big concern here. If you have a test that's not accurate and I do a finger stick on you and it comes back 70, is that really 70 or is it really in the realm of the moderate hypoglycemia or severe hypoglycemia? That's the crux of it.

MS. McCOLLISTER-SLIPP: So, I mean, based on just that statement, sort of taking it in a vacuum, I would be very -- I mean, I want to say, this doesn't work, we need to have

better standards; clearly, capillary blood flow doesn't work for people, particularly people who are unconscious or really sick and may not be able to have any of the symptoms associated with hypoglycemia. But I also realize that by doing that, there are going to be implications, and I don't really have a good grasp of what the potential risk would be that would be introduced because of the implications of restricting capillary-based glucose testing.

DR. BREMER: Dr. Cassiere and then Dr. Wyne.

DR. CASSIERE: Yeah, so just one quick follow-up to that. So we have to talk about cause and effect. There's no data that that caused the mortality. It's related, and that's one of the things in the FDA document I didn't like. It said, "caused mortality." There's no causal relationship that we know of yet. It infers that there is, and I can highlight that there were some patients in that study that did not receive insulin, and they were hypoglycemic because they were critically ill, which goes back to one of the first statements I made to the Panel. I've taken care of over 20,000 patients. I have never seen one of these patients die from hypoglycemia. I've seen them die with hypoglycemias.

So hypoglycemia may be a marker of poor metabolic reserve, unknown liver dysfunction, a whole host of things, so I don't want to relate the two, the cause and effect. I should have clarified that with my statement.

DR. BREMER: Thank you --

MS. McCOLLISTER-SLIPP: But -- sorry. I'm violating all the rules here. I was just going to say, we also knew that --

DR. BREMER: That's okay. A quick reply, and Dr. Wyne to have her chance.

MS. McCOLLISTER-SLIPP: Just quickly, we also know that, I mean, just because you don't die from hypoglycemia, or with it, that hypoglycemia does create stress on the heart and can cause -- you know, maybe it wouldn't happen during that episode of hypoglycemia,

but it could be the next day or contribute to overall weakening the condition -- patient's ability, particularly if they're that compromised, so it's important for a bunch of reasons.

DR. BREMER: Thank you.

DR. WYNE: Thanks. Kittie Wyne.

You know, the data you quoted from NICE-SUGAR is very important, and I would argue that that data had a global impact on hospital management of glucose. And that data is one of the primary reasons why we target a higher number and in terms -- and the most important point is, again, you can't bring cause and effect from it. And you've worked in a critical care setting. You know when someone is so critically ill that their hypoglycemia is most likely due to the fact that they don't have the glycogen stores to maintain their glucose. It's not because you gave them insulin. It's not because you could not accurately measure their sugar.

And in someone that critically ill, you're verifying their finger sticks with arterial or venous, if you're even doing finger sticks at that point. So, you know, it comes back to the issue of what we always struggle with. It's the performance of an assay, the statistical significance of the performance of the assay and the clinical relevance of the data that we have from it.

So I would argue to some extent, clinical practice has already changed to maintain glucose in the hospital, specifically in the ICU but not just the floors, in a safe range to adapt to the lack of accuracy of the blood glucose meters that we currently have. It doesn't mean we shouldn't be concerned about this issue, but some reason -- that's a piece that we have changed our clinical practice, and there's global awareness of that issue, at least in the critical care setting.

DR. BREMER: Any other comments?

(No response.)

DR. BREMER: So I'm going to -- yeah, please.

Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

So, what if we try to approach this as a multi-step process? Because we have to start somewhere, right? So we have seen data when unselected population was tested, and the results were substandard. So we need to come up some kind of limitation to begin with, so let's start to come up with something. Let's give something to the FDA and to the companies that they can test to, they can test that population, and maybe they are able to get clearance for that, and then let's try to expand it.

I agree, for that we need data, but current data says that if you test unselected population without limitations, it will not work. So let's try to work out a first set of limitations, and maybe at this point, maybe it's more conservative because we just need to kind of go according to what's reasonable or what we already know. And that's a first step, and then we will take the second step when the first step works. That would be my recommendation.

DR. BREMER: Thank you.

Dr. Cassiere.

DR. CASSIERE: So I'm going to piggyback on that. So I guess what you're talking about is patients in the intensive care unit with vasodilatory shock. We should probably not use capillary blood, right. Patients in the ICU who are hypothermic should probably not use capillary -- things along that line to give the FDA some kind of guidance.

But the problem I'm having with that is the studies that we looked at, the ICU is in a black box. We don't know who's in there, so we're going to have to recommend to the FDA, well, we think the people in this black box who are inaccurate with finger stick glucoses are the vasodilatory shock patients, come up with a list, so at least if they can get a waiver, it'll

be in the patients in the ICU who don't have these physiologic deficits.

DR. LAKOS: Just to respond to that, maybe we can even approach the people who did the original study. Maybe that information is actually available -- these are patients who were inpatients -- and that retrospectively we can look at reanalyzed data. If we exclude those patients who would be the limitation group, do we get better results?

DR. BREMER: Please.

DR. CASSIERE: So that article I told you about, they broke it down into what subtypes of patients, so I brought up the vasodilatory shock because a lot of these patients had vasodilatory shock. They were more likely to have moderate hypoglycemia or severe hypoglycemia. Patients who you're treating with steroids in the ICU are more likely to have moderate to severe hypoglycemia. Patients with cardiovascular instability, so there are some directions in the literature already, and I would recommend looking at that article in the *New England Journal of Medicine.* It's a nice table that breaks down the patients who are at risk. It's not perfect, but at least there's something to hold your hat on.

DR. BREMER: Dr. Tung and then Dr. Rej.

DR. TUNG: I worry you're going to tie yourself in knots defining cardiovascular instability, defining vasodilatory shock, even defining cardiogenic shock. Definitions for all of those three things vary widely among hospitals.

DR. REJ: Yeah. I was going to have a similar comment, that keeping a checklist of who we go -- maybe I can do it on this person, maybe not. I think that's going to be difficult to implement, but it's a step.

DR. TUNG: Well, shock is a general term. And if you want to be very specific, then you're going to put yourself in the corner, so I would leave it broadly. I mean, hypothermia is easy to define. Shock may not be easily defined, and there is literature to show that if you're on pressors, you have decreased capillary blood flow and there's decreased -- and

unreliability of capillary blood. So that stuff's known, so why not just take that and run with it and not go down a whole checklist of what kind of shock do you have, distributive, cardiogenic? Leave it to the clinicians who are at the bedside to say, yes, this person fits into that criteria. But at least the FDA can have some guidance in terms of what we think should be included in that list. It may not be everybody but -- and that gives the clinician a little more power.

DR. BREMER: Thank you.

Dr. Lias.

DR. LIAS: It would be helpful to understand the information being used to say that those are the patient populations you had described. When, you know, when you make -- if you're making a recommendation to describe certain patient populations that should continue to be limited, if that ends up being part of a recommendation, it would be helpful to know the basis of the recommendation. Just -- the data we presented doesn't show those types of patterns. That doesn't mean they're not there. You know, it's just not in this dataset or wasn't assessed there, but it would be helpful to know what to point to in making those decisions.

DR. BREMER: Thank you.

Yes, Dr. Cassiere.

DR. CASSIERE: Yeah, so not the data you showed us, but data available in the literature. There's data on hypothermia. There's data on pressors. There's data on, I just said, about the vasodilatory shock.

DR. LIAS: Yeah. My interest, though, is in the patients that you would now be saying it is okay to use.

DR. CASSIERE: Oh, so hypothermia is easy. If your temperature's greater than 35 degrees Celsius, you're not hypothermic anymore.

The shock one is a little more difficult. The shock one you could wrap pressors around and look at the literature and look in the literature that looked at the pressors used and what thresholds. And you can go through, and there's been a bunch of articles looking at this in the ICU.

DR. LIAS: Thank you. That's not what I meant, though, actually. I just meant that in the datasets we have, we have data showing that, you know, there were inaccurate results across the population. There was not a pattern demonstrated by condition or medication or things like that. So I'm actually wondering, so you've identified a set of things that you say in the literature it's known that it might cause these issues. What about the other populations that would now be permitted? Do we have data to show that the data would be different in those populations?

DR. CASSIERE: I see what you're saying. So what you're asking is you're asking the opposite of what I answered. So, again, I'm going back to that black box of critically ill, and were the studies large enough and more of an *n* to really show a difference between the subpopulations? So, for instance, I can go to the bedside and see someone who's in shock, and I know the capillary blood flow, capillary glucose is not going to be reliable in that patient.

And, again, not all shock is the same. So to answer your question, there's no data to support using it in other patients except for the clinician's experience. So that's where I meant the leap of faith with the FDA may have to have the clinician involved in the decision of if capillary blood glucose is going to be helpful, because you could think of a whole bunch of patient scenarios that you can't translate into an algorithm or a table that may make a difference. Oh, it's okay to use capillary blood in this patient population, but I may go to the bedside and say, you know what, it's probably not, but that -- so that gives me the leeway of using it or not, based upon experience.

DR. LIAS: Thank you. Recommendations on the types of claims or labeling that you would recommend would be helpful there. You know, broad labeling that just permits everything, labeling that has specific limitations in it, or labeling that has particular mitigations or statement, you know, other suggestions, that would be helpful.

DR. BREMER: Thank you, Dr. Lias.

Dr. Wyne.

DR. WYNE: You know, one of the questions -- I know you said the databases that you guys have showed that there was no association to whatever parameters they tried to correlate to. But thinking about what has just been said, there's probably three specific ones that could be of value that they may not have looked at: So one is body temperature; one is specific use of vasopressors at the time of the measurement; probably the other one would be mean arterial pressure.

And the question is, is it possible to ask those databases, do they have those three specific factors, and could they go back and sort by that?

DR. LIAS: I doubt they do in these cases for the studies because they were performed to assess the glucose meters, but if the Panel wants to recommend certain things, we could certainly keep those things under consideration.

DR. WYNE: I mean, if we wanted to give parameters for use in making the clinical judgment, it sounds like those are probably the three that you could use. Unfortunately, capillary refill and presence of edema are a little bit more subjective, so it'd be hard to use. And if you're not giving a specific number but you're just saying that using these three factors in making the judgment, I don't know if that's even too vague. But, you know, those sound like the things that need -- that's what we use as the basis of our clinical judgment is what I'm hearing.

DR. BREMER: Yes, Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: One other question. There may be others, but for now just one.

We talk about intensively managed or intensive medical intervention therapy. I mean, there was some discussion in public comment that that's not something that's particularly well defined or consistently defined from hospital to hospital, which is, you know, an issue for somebody like you who is trying to create, you know, rules about how this stuff gets used. But I also wanted to reference -- it wasn't me, but a friend of mine who has Type I who actually works in the medical device business, when she was having her second child, was convinced that she had really severe hypoglycemia as she was giving birth. And they kept testing her with a point of care device, and it kept saying you're normal.

And she kept saying I think I'm really low, and you know, they kept arguing, saying, oh, it's because you've got all this other stuff happening, you can't trust your symptoms. So she asked them to do a venous glucose level, and it came back at like 22, and so perfectly healthy, healthy pregnancy. I don't know what the implications of having a child when you're severely hypoglycemic are. Her child's fine, but I think we need to think about -- and I don't know what sort of medical things could make that an issue with capillary blood flow or if it was just a bad day for that testing equipment, but that is something that we would need to consider in terms of, you know, different hospitals or CMS or whomever it is going to be interpreting this stuff.

DR. LIAS: Courtney Lias.

You remind me of something we didn't go into, which is some of the history behind the terminology and the labeling. So we didn't really go into this, but obviously, you can tell that the term "critically ill" was much objected to. So that had been sort of used as a vague term, and many of the -- and understandably, in the lab community, said what does that

mean? And there was no definition, and so there was a lot of discussion about what does critically ill mean? POCT17 was started to try to help hospitals have a more uniform definition.

The labeling that went into Nova, which is this wording that we've been using, was developed because they went out to clinicians and asked them what type of description would you use to describe this population, and that is the wording they came up with. So it is very tricky to develop labeling that is specific enough and provides guidance, so maybe that history is helpful as to where the wording came from in the labeling.

DR. BREMER: Thank you.

Are there any comments?

(No response.)

DR. BREMER: I'm going to try to -- I think this has been a robust discussion, both this morning and just now, and I think it's robust because there's no easy answer. I'm going to try to summarize for the Panel, kind of highlighting the four points that the FDA has asked us to address. That said, I welcome edits and I welcome suggestions. We have you here today, and I would love to be able to provide the FDA some of the guidance that they've convened us to provide.

So as far as the assessing the factors that -- as far as risks and benefits of using glucose meters and capillary blood glucose in those receiving intensive medical intervention and therapy, I think the consensus I've heard this morning is the benefits are the potential ease and the rapidity with which to receive potentially clinically useful information in the hospitalized setting to make a medical intervention. And I think that the point of care devices, I've consistently heard today, many times, you get a quick answer, and it's easy to do by myriad healthcare professionals.

That said, going to point (b), the potential risks are how to interpret that data, and is

the data obtained on the point of care device gathered from a patient that is quote/unquote "suitable?" And I think the things that I've heard throughout the table this morning are how to best provide guidance on defining who those participants may be, and so we have to -- saw that -- we heard that participants are not all equal and that those in various stages of shock or hypothermia or other more life-threatening situations may not be amenable to monitoring via capillary blood glucose, whereas those more stable may be. And maybe one of our tasks is to get more granular about conditions that can be useful to the FDA, whereas not too restrictive.

As far as potential mitigation things, Dr. Wyne brought up the example of the BRAVE acronym and kind of systems that could be put in place, potentially put in place in hospitalized settings to potentially mitigate any untoward event of using and interpreting a capillary blood glucose measure for a medical intervention.

And then I think the thing we're all struggling with is how to balance the potential risks with the potential benefits, knowing that there's a lot of subjectivity in clinical management.

I didn't -- you'll notice I didn't provide my opinion or a strong opinion, intentionally, but is that kind of the -- which, clearly, I want that to come from you. Is that kind of a succinct kind of summary of where we are?

Yes, Dr. Lias.

DR. LIAS: I don't actually understand what you said about --

(Laughter.)

DR. BREMER: That is absolutely fair.

DR. LIAS: -- about (c) and (d), so it would be helpful to hear a little bit more detail on the Panel's consensus for those.

DR. BREMER: So I'll try to reiterate maybe this a little bit more succinctly and then

open it to the Panel.

As far as the unique risks, I think that's where I identified there are certain patients in the hospitalized setting that may -- they, because of their clinical condition, may be more clinically suspect to having a nonreliable capillary blood glucose measurement, whether it be on the floor or in the ICU. And so doing a clinical -- as far as mitigation, doing a clinical assessment prior to doing a capillary blood measurement may be one potential way to mitigate an untoward interpretation.

DR. LIAS: Can you clarify the type of clinical assessment that might be needed? And is this something that would be in the instructions of the device or something handled in another way?

DR. BREMER: So I'm going to open that to the Panel. I'm going to steal the example of the BRAVE acronym from Dr. Wyne, but I will open that up to the Panel. I think it's a great question.

Dr. Cassiere.

DR. CASSIERE: Yeah, so just a -- the MAP, right, a mean arterial blood pressure greater than 65 on no pressors, I think we'd agree to that. I think we'd also agree to the normothermia. That would be another issue. And the other issue would be assessment of capillary refill. Again, everything that Dr. Wyne said, I want you to jump in and use what you use at your facility. That could really be a help.

DR. WYNE: And this is Kittie Wyne again.

One thing -- I looked it up during lunchtime, and when they had first started the BRAVE criteria, it was just blood pressure above -- below -- above 80. But they discovered in our heart hospital, blood pressures were always below 80, so they switched it over to blood pressure or MAP. So the MAP, you know, you're -- but the key is the other one is just if they're in acidosis, because acidosis is a problem too.

But I think the biggest ones are blood pressure, temperature, and the use of pressors. I mean, there are other, lots of things we could raise, you know, hemodialysis patients, all that. But just as a very broad criteria, I think those are the --

DR. LIAS: Is the recommendation that the device be limited against use in patients in some way?

DR. WYNE: Who meet that -- yeah.

DR. LIAS: Or is this a recommendation for something different?

DR. WYNE: I think it's more of a consider not using it in a patient who is in this kind of clinical scenario.

DR. LIAS: So that's what I'm saying. If we put that in the labeling, it would be considered elimination. You know, this may not be appropriate for use in these patients, which would be considered the off-label use if somebody did it. So I'm just trying to understand, is that the recommendation? And then is that a recommendation for the manufacturers to study populations that don't have those people in them and then if they get the same data?

DR. WYNE: I would say, absolutely. The people who don't have those issues are the ones we want studied so that we can have it demonstrated, you know, that their capillary blood glucose can be used.

DR. LIAS: So --

DR. WYNE: That's where you bring --

DR. LIAS: One of the questions we have -- and that's very helpful because we can go down, you know, those discussion lines -- one of the questions we have, though, is if you can't identify as a population -- say they did study the patient population without those people in it and you still got the same data we presented today. Are there considerations that we should think about in terms of the benefit-risk balance if the population you're

testing has that performance?

So, you know, we could limit a population, and maybe this is the right population to limit, and you end up with data that looks more like the arterial and venous data. That's clear. If you limit these people and it's still similar to what we showed today, are there considerations that we should keep in mind?

DR. WYNE: I think what would be valuable is if, as a group, we gave our other clinical impression of the people we're hesitant to use capillary glucose on so that the manufacturers could realize that those are factors they need to take into consideration. You know, capillary refill is something that can be used, presence of edema. The big one to me is dialysis patients because they often have poor circulation, but maybe we could weigh in with some suggestions there of what could be evaluated for the future, not necessarily into being that restrictive right now.

DR. LIAS: Yeah. My question is, actually, if we see the data that we saw today -- and you might not be able to weigh in on this but --

DR. WYNE: No.

DR. LIAS: -- our question is, actually, if the capillary blood data presented to us in a premarket submission were the data that we presented today, what are the benefits and risk? What's that benefit and risk balance, if that is what is done, you know, if that's the data that is generated in your setting, on label?

DR. WYNE: So that's where I'd say, you know, in terms of the clinical benefit, what I'm hearing from all of us is we feel that the clinical benefit, if used appropriately, is valuable even though statistically it doesn't meet the numbers we want.

DR. LIAS: Okay. And it outweighs the risks, in your opinion?

DR. WYNE: Yes.

DR. LIAS: Does -- it would be helpful to understand if that's the general consensus?

DR. BREMER: So I'm going to -- we have -- this is great. This is the discussion we need, so Dr. Cassiere, Ms. Lee, and then Dr. Lakos.

DR. CASSIERE: What I was just going to follow up on is that maybe in that population that we're concerned about, they need to do a confirmatory test and then use the finger stick. And I agree 100% with the comments made. I think it's -- the benefits overwhelmingly outweigh the minimal risk.

DR. BREMER: Ms. Lee.

DR. LEE: Rosemary Lee.

Two things: I'd like to reinforce about the edema, the peripheral edema and, you know, not accuracy then. I've seen nurses do that on people that look like Michelin men, and you're not sure how much blood and how much interstitial fluid you're getting, so that's one concern. Another concern I haven't seen addressed but I have seen this in my unit, patients who are prolonged in the ICU, getting insulin on regular intervals, so that their fingertips are mottled or so black and blue. Is there a point where we say don't do that anymore? So I think that needs to be addressed, because I do believe we're causing damage to those poor little fingers. Thank you.

DR. BREMER: Dr. Lakos and then Ms. McCollister-Slipp.

DR. LAKOS: Gabriella Lakos.

So I have been involved in designing and managing clinical studies, and from a study design point of view, what I would do, I would do a bigger study, less restrictive, maybe unrestrictive, unselected population. And it's just a matter of statistics to do a step-wise exclusion. Exclude this, exclude that, look at the data, recalculate, and maybe -- as I said, maybe we can do it retrospectively with the existing data. If we are lucky, those data are there, just need to be accessed.

DR. LIAS: This is Courtney Lias.

That is what they did. That's what they looked at to try to understand whether they could find any particular populations that had different performance.

DR. LAKOS: But I didn't mean population. As we discussed, shock or surgery or cardio, it's not an objective measure. If we say blood pressure of 70, if we say body temperature of XYZ, that's a different type of categorization. There are two surgeries that can be very different, and clinical conditions, based on the clinical condition, it can be very different at a patient level.

DR. BREMER: Please.

MS. McCOLLISTER-SLIPP: The question, coming at this from the perspective of a patient as well as the daughter of a patient who, again, just got out of ICU yesterday, I'm just trying to understand what are the risks? So if we put restrictions -- or obviously not me, but if we recommend, you know, that you restrict the use of capillary blood tests in intensively managed patients or whatever, so if that happens, then what happens in that hospital room, and what are the potential risks that are introduced by doing that?

So I'm picturing myself sitting in either my hospital room or my father's hospital room and, you know, I test his blood sugar with my meter, or his meter, and it comes in low. And I, you know, grab the nurse and say, hey, I think we need to put some glucose in his thing, and she's like, well, I can't do that because I have to get so-and-so from the lab to come in and get a venous blood draw up and etc., etc. I mean, I don't know what the specific procedures would be. And then that person's busy, so it takes 45 minutes, and I'm sitting there watching my dad go lower and lower.

I mean, is that a possible scenario that could come up? If so, that could be a much bigger risk than the potential of having a slightly inaccurate or 85% accurate capillary test.

DR. BREMER: Dr. Lias.

DR. LIAS: Yes, so I was also wondering, for the users in the room, compared to the

current limitation on capillary blood -- because I'd like to remind you all that these meters are available, and the limit -- and they're cleared for capillary blood use in all other populations in the hospital. The limitation is on that population right there. If we were to change the language and limit this other list of things, is that a meaningful difference to the user or the laboratory? And I don't know the answer to that. Is that a meaningful difference than that exclusion? And that's what I -- it would help to know.

MS. McCOLLISTER-SLIPP: And I would say how does that impact patient care? You know, the situation that I just -- is that a possible scenario? And if so, then I would say that introduces significant risks.

DR. BREMER: Ms. Kirkpatrick.

MS. KIRKPATRICK: Sherry Kirkpatrick.

I think, as Dr. Wyne pointed out, the three criteria with the normothermia, the mean arterial pressure, capillary refill, as Ms. Lee said, or DKA, just those four things, nursing judgment would note, capillary is not appropriate. So as a bedside nurse, whether you're associate degree level all the way through master's, that's basic nursing judgment, that we could use that criteria.

DR. LIAS: So that would be easy to identify.

DR. BREMER: Any other comments?

Dr. Lias.

DR. LIAS: I just want to confirm what I think that I heard, and then you can summarize. But based on my question of if the data actually did look like this in whatever population ended up, it sounded like the people who weighed in thought the benefits still outweighed the risks. Can you confirm that that's the consensus?

DR. BREMER: That was my recollection, but I'll ask for clarification for anyone. I guess my nugget summary, and I'll keep it -- was, is that there are risks that we've all

identified, but I think, overwhelmingly, the potential benefits of point of care use in capillary blood glucose monitoring in hospitalized patients outweighs those risks, and I think one of the things we're challenging is how best to mitigate those risks and how best to define those at highest risk. Is that adequate to the Panel?

DR. ASTLES: This is John Astles. I'll just reiterate the comment that there should be some confirmatory testing. I think that was mentioned.

DR. BREMER: So would it be --

DR. REJ: Yes, and I agree with that.

DR. BREMER: Dr. Rej.

DR. REJ: Yeah. This is Bob Rej.

Clarification: In your question to the Panel, if we were to accept that decremental performance shown in the studies this morning, correct, was that acceptable? I think that's really hard to answer because you have to tease out those populations that we just talked about. And if that could be done, then I'd feel more comfortable with that recommendation because right now they -- I believe it was all in critical care or some, you know, large umbrella. And if you could tease out those that are, you know, hypothermic, whatever, the lists that were presented, then see what the decremental accuracy would be in those populations after you removed those that some revised labeling would address.

DR. LIAS: This is Courtney Lias.

So do you mean that you believe that if you take those people out, you would see better performance, because what I was actually asking is -- certainly that would be better.

DR. REJ: It's --

DR. LIAS: If you didn't see better performance --

DR. REJ: I think it's a possibility.

DR. LIAS: Certainly it's a possibility.

DR. REJ: Yeah.

DR. LIAS: But our actual question is if we're faced with this data in any population, do the benefits outweigh the risk? And I think I did hear that it --

DR. REJ: I would have some concern. You're doubling the number of results that are outside a specified limit, and that, to me, strikes me as being a big difference. You're doubling it, so I'd like to see what performance improvement you get if you remove a certain class of patients and whether that number goes down to something that may be insignificantly different from those who have basically normal capillary blood glucose.

DR. BREMER: Thank you, Dr. Rej. I think one of the things that we struggle with and we're limited by is the data that we have, and that's the challenge. So one other thing that I will approach the Committee is do we recommend that, moving forward, you know, these patients that are hospitalized, should they be more systematically -- should we be recommending that there be more systematic study of hospitalized patients using meters to -- it was brought up, to get more data, to make clinically informed choices or data-driven choices versus what we have to date?

Dr. Wyne.

(Off microphone comments.)

DR. BREMER: Oh, I'm sorry.

Dr. Astles.

DR. ASTLES: Quickly, I'll just say, I'd like to see more data, of course, and I'd like to see what direction the data -- which direction the error is, you know. If we're talking about hypoglycemia and the error is in a certain direction, I think that might influence FDA's decisions.

DR. NIPPER: This is Nipper.

I just agree with Bob and John about the more data, and I'm particularly interested

in the data being driven by the BRAVE criteria, to see how that differentiates people who are at higher risk from people who are not higher risk. And if you get bad -- if you get a glucose on somebody, capillary glucose on somebody who meets those BRAVE criteria and you deliberately go ahead and check that against a venous or arterial number to verify what it is, it's really interesting to see -- it would be really interesting to see how many of the people who meet the BRAVE criteria don't check and how many who are outside of those BRAVE criteria do check.

In other words, do that 2 by 2 table, do the grid, and see how well those criteria work, and then you've got objective clinical criteria that you can use.

DR. BREMER: Dr. Rej.

DR. REJ: So we're asking for more data.

DR. NIPPER: Yes, because I don't think you have enough.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: I'm going to concur that we need more data. We all know what a perfect experiment should look like. The question was, given what you have, what you can do with it, right. And I think pretty much heard the opinion that the benefits, you know, outweigh the risks but, at same time, that there needs to be a consideration to a specific measurable criteria which can be determined at bedside in which you should consider rechecking, calibrating, using some other method.

DR. BREMER: And so is it a -- oh, yes, I'm sorry.

Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

What we don't know is the level of error in that population that can potentially be affected, because we see numbers, but behind those numbers there are patients. And if -- let's say in 5% of that population that the results are grossly inaccurate, so I think when we

are talking about more data, we also need to assess not only whether if we exclude this population, is it going to get better? And in that, how does it look like in that particular population where we think there is the risk? So I don't think we know how much the risk is at this point.

DR. BREMER: Thank you.

Dr. Wyne.

(Off microphone question.)

DR. BREMER: No. This is my blind side over here on my left. Dr. Tung then Dr. Wyne.

(Off microphone comment.)

DR. TUNG: I was going to say, I fully concur with the need for more data. I think we're guessing when we argue that patients below 35 are going to have bad glucose measurements and above 35 are going to have good ones. I think that's just a straight out guess.

Moreover, I'm not so sure, like if they're 34.9, then that's good, and they're 35.1, oh, we can do it now. That becomes very, very murky, and the same is true with edema, which can come and go and is very difficult to assess.

In a way, you know, right now the system works because the hospital knows that the burden is on them to not screw up, given a system that is not very accurate. Hospitals have all kinds of monitoring systems to figure out who's going to do one, who's not. One example is which surgeon did the case? There is a monitor that may not be very accurate or may be, but you know, sometimes you think about that. By assuming the responsibility and saying we declare this safe and, you know, clearly of benefit, in a way you're taking the responsibility off the hospital by saying, yeah, it's safe. We're saying it's safe; go ahead and do it. I do worry that until we know exactly what is and is not safe, there's a lot of

guesswork.

DR. REJ: And, Dr. Tung, you're saying to the hospital, no harm's going to come to your patient from an erroneous glucose measured in this device, which is -- that's up in the air, I think.

DR. TUNG: Maybe you're just saying that the harm is not your fault.

DR. BREMER: Yes, Dr. Wyne.

DR. WYNE: So I have a question that I don't know if maybe I shouldn't even ask it, or maybe I've already answered it. But with the data that we currently have available to us, if we were to make an assumption that is absolutely an assumption with no data whatsoever, that the people we've been referring to were not included in that population, in other words, the people who were hypothermic, on pressors, if we were to make that assumption, would we feel comfortable using this data then to say these devices could be used on the rest of the population? Does that make sense? If we assume that those people were excluded, is this data sufficient?

DR. BREMER: Well, I think that is -- yes.

Dr. Astles.

DR. ASTLES: I would just submit that we would want to know the magnitude of the errors. We know a certain number outside, but we don't have -- all we have is summary data.

DR. WYNE: So what I'm saying is, you know, what about the possibility that the errors that are there are not due to people who should not be getting capillary in the first place? So, from a clinical perspective, is this acceptable for what I need for my patients in the hospital? Do you see what I'm saying?

DR. LIAS: Yeah. That's the question I was trying to ask, and you said it more eloquently than I did.

DR. WYNE: Oh, thanks. I mean, my -- you know my answer, which is it is sufficient to me, but I'm assuming that my nurses, my intensivists have the clinical judgment to not do it on the patients we've been talking about.

DR. BREMER: Thank you.

Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: I mean, as a patient and the daughter of a patient, I would say it absolutely is not sufficient. But compared to what is sort of what I keep coming back to. I mean, compared to perfection, no, it's not sufficient. It would be ideal to have capillary or venous, you know, blood testing for all hospital-based decisions. But I still don't have a clear understanding of what the implication of something like that would be in terms of work flow or in terms of slowing down access to more, you know, rapid treatment of a potential hypo.

So that, to me, is sort of the crux of the thing, is like are we introducing more risk by trying to mitigate it? And I still don't have a clear sense of that because I don't work in a hospital, but I can just picture my head exploding, sitting next to my father's bed, waiting for somebody to find the dude from the lab to do the test the way it's supposed to be done when I am sitting there with, you know, my arsenal of different glucose measurement tools, so -- but, again, I don't have the ability to assess that. I can just say I don't want to introduce more problems by trying to fix them.

DR. WYNE: Can I comment on that?

DR. BREMER: Please.

DR. WYNE: This is Kittie Wyne.

So if I'm in the ICU and seeing a patient and a family member has a concern, and I'm waiting for a confirmatory glucose and the family -- and this is me, speaking my personal practice, the family says, can I use my personal glucose meter? Now, the hospital doesn't

accept that, and this has always been a debate in hospitals; what about people using their own? I would never stop you from using your own glucose meter. If nothing else, I would encourage you because you're checking your accuracy against our laboratory device.

So in terms of, you know, the patient concern of is this going to delay finding hypoglycemia, I don't think so because I think we're going to be checking the person. We're going to do a finger stick if we think that that's what's causing it at the moment, and we'll send a confirmation, but I wouldn't stop you from checking with your own meter in any scenario.

MS. McCOLLISTER-SLIPP: But what if I'm not there? What if the patient isn't --

DR. WYNE: Well, but that's the risk of anybody being in the hospital, and we can't control everything, but we can develop a well-trained intensive care unit staff to try to mitigate as many risks as possible. We can't prevent everything.

DR. BREMER: Thank you. Other comments?

(No response.)

DR. BREMER: I want to keep us on track and keep us focused on this difficult question, and I think we were struggling and somewhat talking in vague terms because of the lack of data that we all want more of, to make a more informative choice.

Dr. Cassiere.

DR. CASSIERE: Well, along that line, I guess the patient's the best control, and I'm going to reiterate the confirmatory tests on a patient who you're concerned about capillary blood glucose. Let the patient be their own control, so if I get a capillary glucose that's within the range and then I get a venous or arterial and it's in the range, I can at least -- I've gone to another level of safety to assure that at least that finger stick that I'm going to do is reliable. Now, again, patient situation changes, but we don't live in a perfect world, but at least that's a start.

DR. BREMER: Ms. Lee.

DR. LEE: I just have a general question. When you're using the patient as their own control, what's the acceptable variance from what the capillary is to what the venous or arterial is?

DR. CASSIERE: So I can tell you, in a few of our ICUs, it's within 15%.

DR. BREMER: Thank you, so also what I'm hearing -- and, again, I'll try to be -- I will be brief because I know we have more to discuss -- is that there is consensus that in this population there's a tremendous benefit of having these devices available, recognizing all the potential risks that we've discussed and all of the clinical scenarios that may impact the reliability of interpreting that capillary blood glucose measurements, and the want for more data moving forward but being stuck with what we have right now to be informative to the FDA.

Is it also fair, based on the discussion this morning, a lot of people on the Panel had mentioned the need for increased either education or the promotion of the potential limitations of interpreting capillary blood glucose values in hospitalized patients, not being necessarily overly granular or being too specific but disseminating what we know now as to the general public. You know, the question came up, is it -- do people know that there are potential problems in interpreting blood glucose? Would increased education and/or other ways to impart this data be something that the Panel would recommend? Or not? Or do you think that this is well known, the limitations of capillary blood glucose?

Dr. Cassiere.

DR. CASSIERE: I would just broaden it. The new vogue in critical care now with septic shock is vitamin C. These patients are getting grams of vitamin C intravenously. Not many clinicians are aware of the discrepancy with ascorbic acid and glucose testing, so I think education is always important. And I wouldn't assume that clinicians know about

acetaminophen, vitamin C, or any other pitfalls with point of care testing in general, not just specific to capillary blood.

DR. BREMER: Yes. Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: Just for color commentary, I'd like everyone to know that I have a CGM reading that seems a little off, so I'm using capillary blood testing right now to confirm that that actually makes sense, so just for context.

DR. BREMER: Thank you.

Any other comments on this question? Yes.

DR. ASTLES: John Astles. I do think that education would be important. I mean, I think even this Committee was surprised at the low accuracy, and you all are well-informed experts in this area, so I would vote whatever we can do to get word out to clinicians that capillary blood testing is apt to be inaccurate in certain circumstances.

DR. BREMER: Thank you.

Other questions? I'm going to ask Dr. Lias.

I don't think we were able to give complete, grounded guidance on what to do, but I think that's only because this is an area where there's a lack of a lot of information to be overly informative. Was our discussion, Dr. Lias, helpful and informative to you?

DR. LIAS: Yes. Thank you.

DR. BREMER: Thank you, and thank the Panel.

Again, I think this is -- I encourage you all, beyond this meeting, to continue thinking about these questions because this is a very important, clinically meaningful area where there's a lot of subjectivity and a lot of clinical judgment, which is always hard, as has been said. It's very hard to capture in a bin, clinical judgment. Okay.

So now we will move on to the second question, and again, this is where I -- at the outset, we talked about kind of clearance and usability of these devices versus a very

separate question, which is the issue of CLIA. And the reason I asked for the clarification of the differences between CLIA waivers via a moderate indication is that those are different, and they have implications, and so I invite the Panel to address and voice any comments regarding this question.

Dr. Cassiere.

DR. CASSIERE: I have a problem with handing the glucometer back to the PCA or the non-RN, and I'm for the waiver, but I'm also for keeping something tight around this process because it's a high-level intensity process that needs expertise. But yet we want to use it freely in the intensive care unit, and that's why I asked that naive question, if you have a CLIA waiver with special controls, and maybe we need to start thinking outside the box because this is a very atypical situation.

We have clinical circumstances in the ICU. The data on hypoglycemia control is rock solid: mortality benefits, decreased infections. That's unshakable, and we have the availability of testing at the bedside, real-time, adjusting the drips. Going back in time or having a test that now is going to take me 15 to 20 minutes or 30 minutes to adjust is not good patient care in my opinion.

So we need to figure out how to break this, and that's why I throw out there this waiver with special controls, like some of the Class II devices are approved with special controls. I want my lab to stay on top of who's performing it. I want quality control. I don't want just to throw the device out there, let anyone use the device, not in the ICU.

DR. BREMER: Thank you. Other comments?

Dr. Nipper.

DR. NIPPER: If everybody felt the way you do, I wouldn't worry about it as much as I do, but I'm not sure that your professional controls are in place all over the place. Dr. Wyne has been assuring me that it's better than I think it is, but I'm not as optimistic.

DR. BREMER: Thank you.

Dr. Tung.

DR. TUNG: It sounds to me like Dr. Cassiere is recommending a moderate-complexity level of regulation. No?

DR. CASSIERE: I'm recommending the free use of a device that has controls around it, but they're not arduous controls and do not place an unnecessary burden on the healthcare providers, and that's my sneaky way of getting out of that.

DR. BREMER: Thank you.

Dr. Lias.

DR. LIAS: It would be helpful if you have an idea of the types of controls. If they're a high school degree, proficiency testing, quality control program and inspection by CMS, then that's pretty easy to do. If they're other things, we'd have to, like you said, figure out if there are ways to do it.

DR. CASSIERE: Well, the first thing I mentioned early on is do a correlation study. Your lab should be required to do a correlation study with your glucometer in finger sticks and correlate them with the venous samples. And then there should be how often the nursing staff needs to be re-educated, signed off on. And I think there's ways to put brackets around that without making it a moderate-complexity test.

And that's above and beyond my knowledge. I'm going to ask my laboratory and pathology people what you guys think should be in place so that we can use this device but, in your opinion, use it in a safe manner that has some quality control involved.

DR. BREMER: Dr. Nipper.

DR. NIPPER: I don't know whether this will work or not, but I'm brainstorming at this point. But if I did a test in my lab that did not have a recognized proficiency test program, what I'm required to do by the lab inspector is to do specimen comparisons with another

laboratory that's doing the same test so to set up my own proficiency test program. That's what you're saying. In other words, you were saying that in your ICU, you would set up an informal proficiency test program that would be done regularly so that your people and your devices could be compared to the central lab or to the blood gas lab or something else that's doing venous or arterial stuff.

I don't know that that's a bad idea. There may be better ways to do this, but your -- you didn't just -- you just reinvented the wheel there with your suggestion. It's being done all the time now with esoteric tests for which there's no PT, but they make PT for blood gas apparatuses now. They make QC, so in my hospital, we had people do PT and QC regularly to show they could do the work. That was not an onerous burden in my view. It wasn't cheap, but it works.

DR. BREMER: Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

I just don't want to focus on the wrong thing. I think we already stated that the analytical performance of the instrument is not the issue, so I'm all for internal and external quality control, but it doesn't solve the basic issue.

DR. BREMER: Thank you.

Dr. Rej.

DR. REJ: This is Bob Rej.

But if that ICU laboratory comparison were done knowing the patient type, that could give some information on the criteria for exclusion. I agree. I mentioned this morning this is not an analytical issue; it's a specimen issue.

DR. NIPPER: Right. Right.

DR. BREMER: Other comments from the Panel?

(No response.)

DR. BREMER: Okay. I will summarize and invite comment and then make sure I'm going to -- also, I'll try to be a little bit more clear. I think we're stuck on this one as a Panel because I think what we want may not exist, and I will defer to Dr. Lias for that.

But I think we all -- what I'm hearing is the extreme benefit of having these devices at the bedside and accessible for use. The concern is, is the sampling sufficient to provide a value that can be acted on meaningfully, clinically? And whether changing how the CLIA designation is either a waived or a moderate, I think we're -- what I hear is struggling amongst the Panel, is waiving it, having a CLIA waiver too permissive, and is having a moderate designation too restrictive?

Dr. Astles.

DR. ASTLES: John Astles.

It just occurred to me that there is a provision that allows some flexible approach to quality control, and that's the IQCP. It's an individualized quality control planning, so this would mean that the institution reviews all the different attributes of risk and then decides based on that. It would be a customized approach of how often do individuals need to demonstrate they can get the right answer, and sort of, if you think there's some areas that are higher risk, you know, you can, within the hospital system, you could do something special for them and special for certain operators and so forth. This is a very flexible approach that QNS has been -- it came out a couple of years ago.

DR. BREMER: Thank you.

Others?

Yes, Dr. Rej.

DR. REJ: Yeah. One probably last comment: I think the automatic classification of a modification to a waived device automatically going to high complexity should be looked at. I don't think it should be automatic, and in this particular case, since it's largely a sample

issue, not a laboratory issue, a laboratory oversight issue, I think that that should be considered.

DR. ASTLES: Right. This is John.

DR. LIAS: That's definitely beyond our scope here today.

DR. ASTLES: Yeah. So the IQCP would work for moderate-complexity testing, not -- wouldn't be restricted to -- it wouldn't apply to waived, but it would apply to moderate.

DR. BREMER: Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

I think the other issue here is that when we are talking about waived and moderate and high-complexity testing, we are talking about an isolate laboratory assay. But here, I think that the most important thing is indication and interpretation, so not by performing the test. So the test itself, it is really easy, so we are kind of combining these two issues, but somehow we need to make distinction.

DR. LIAS: Courtney Lias.

So I mentioned earlier, most point of care test or bed-tied tests are moderate actually, so less of them are waived. I wonder if, though, people who use devices at the bedside here might comment on -- you know, we've heard one comment on blood gas analyzers, their experience with moderate-complexity point of care tests, which like I said constitute most of them.

DR. BREMER: Dr. Wyne.

DR. WYNE: I had a question sort of about that, and I think it was raised earlier, but I just keep thinking about it.

So if this is moderate complexity in the ICU, then that means the RN has to run the test. No?

DR. LIAS: The criteria for high complexity would be a medical or laboratory degree.

But for moderate complexity, it's a high school degree and some other things.

DR. WYNE: Okay, because I was just thinking, you know, part of the way the decision's made, at least what I have observed in ICUs in a couple different hospitals, is the nurse is the one who makes the decision whether it's going to be arterial blood or a finger stick. And then the nurse either does the finger stick or calls for the person who does the finger stick for their unit, depending on their structure.

So, again, it's back to the issue of the decision making, but the nurse plays a very important role in that decision making of what type of blood is the source, so I don't think whether it's CLIA waived or moderate really makes a difference there.

DR. BREMER: Are there thoughts on that from the Panel, because I think that is one of the questions we were posed to ponder today.

Dr. -- yes, Mr. Aviles.

HSCM AVILES: Mike Aviles. I would agree with that statement there because it's the team treatment -- it's the treatment team component, and we're going to collaborate the results, or the judgment based on the clinician. So there's always collaboration going on, and we're going to double-check each other most of the time. So I think that staying in that -- it doesn't really make a difference whether it's waived, a CLIA waiver or a moderate complexity, because we're already doing that kind of thinking, that clinical thinking already as a team.

DR. BREMER: Thank you.

Dr. Grunberger.

DR. GRUNBERGER: I mean, this horse has been dead for about a couple of hours, but let's beat it down again, once more. We sort of collectively decided it's nothing but a machine; it's nothing but a device. This is a device division. Why complicate the issue? It should stay waived. And once we talk about it's the specimens, the underlying pathology,

biology, clinical judgment, how would that complicate the bureaucracy of the device itself? And I would leave it up to the individual institutions, hospitals, intensive care units to deal with the training.

We already heard presentations that classy places have it in place already. As you say, it's a team effort, and so I really would not play with the CLIA waiver unless you have the power to change the CLIA criteria, and we focus on the clinical judgment, education, and the underlying pathology and biology of the specimen.

DR. BREMER: Thank you.

Other comments?

Yes. Dr. Tung.

DR. TUNG: I am a fan of proficiency testing. I've participated in myself, as a requirement, a moderate complexity, and I do think it does help the accuracy of the test.

DR. BREMER: Thank you.

Other comments from the Panel?

(No response.)

DR. BREMER: It's always -- it's nice to have a discussion on questions that aren't so clear cut. I think that's where it's nice.

I think I may summarize in a very noncommittal answer, but I do that not to keep flogging a dead horse, but I do want to provide our FDA colleagues with useful information. I think in answer to the question about what are relevant factors, one relevant factor is the actual sampling of the specimen and, moving forward, trying to maybe be creative in how to delineate language regarding use, regarding the actual device versus the sampling and the specimen. And then the need for quality control of how these devices are used and whether a CLIA designation facilitates that or introduces other untoward consequences, I think, is difficult to know right now.

I think we've had a great discussion about the concern about unintended consequences of designations while maintaining every effort at patient safety, and I think that's a very fine balance sometimes. And so I'm not hearing a strong consensus of changing or recommending a certain CLIA designation, waived versus moderate. I hear pros and cons. Or I hear discussions about why each -- or even high for that matter -- could be appropriate based on the appropriate clinical context. Is that incorrect?

So I'm being noncommittal to any answer as I don't think we've reached a consensus, but I want to coordinate our team to realize that there's lots of moving parts in this decision.

Any other comments from the Panel?

Dr. Lias, have we gone around enough for you, to be helpful?

DR. LIAS: Yes, thank you.

DR. BREMER: Thank you for saying that.

(Laughter.)

(Off microphone comment.)

DR. BREMER: That's right.

Now, back to my script. I do want to recognize everyone who spent their time here today on this Friday.

Just going around, are the representatives, Ms. Carolyn Peterson -- thank you for being here -- do you have anything else that you would like to contribute to this discussion?

(Off microphone response.)

DR. BREMER: Okay. Ms. McCollister-Slipp, thank you for being here on Day 2. Do you have any other comments or things that you want us to consider, moving forward?

MS. McCOLLISTER-SLIPP: Nothing further.

DR. BREMER: Thank you so much.

And, Dr. Lakos, again, thank you for being here. Is there anything else that you would like the Panel to consider, moving forward?

(Off microphone response.)

DR. BREMER: No. Thank you so much.

With that, I have the privilege, once again, of having sat here for a second day. I appreciate all of the insightful input from the group. I think these were -- this was a -- these were questions that were posed to us with no identifiable answer and no clear-cut, slam-dunk answer, but I think the discussion today, although it was somewhat circular at times, reinforces how clinically important having access to quick quality testing is for patient care and how we all value the importance of safety and making the appropriate determination of a test when it impacts patient care. And so I appreciate the careful and thoughtful insights for the comments.

With that, I'll ask Dr. Lias if our group today can do anything else before I close the meeting.

DR. LIAS: I just wanted to thank everyone. We don't bring questions with easy answers to an advisory panel, so we recognize that these are not no-brainers, and the discussion today has really been helpful. We've heard a lot of feedback that will help us understand either, you know, how to reach out to people, what considerations might be important, and that's really going to help us as we move forward. A lot of my questions and clarifications were just to keep the feedback coming, and I really appreciate the time you put into reviewing the materials and having this discussion and traveling here today.

And I really want to also communicate how much we understand how valuable these devices are and how we agree that this information should be communicated even more broadly, I think, than device labels. And if any one of you have ideas of how that might also be improved in the clinical community, we're also happy to help with that if we can.

So thank you very much, and Drew, I really appreciate you spending 2 days with us and really managing the process well, so thank you very much.

DR. BREMER: Oh, thank you.

And now I have the privilege of my last scripted statement before I wish everyone a spectacular weekend. I now have the privilege of pronouncing the March 30th, 2018 Clinical Chemistry and Clinical Toxicology Devices Panel for Medical Devices Advisory Committee adjourned. I wish you all safe travels home. Have a wonderful weekend. Thank you again.

(Whereupon, at 2:31 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

March 30, 2018

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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SHAYLAH LYNN BURRILL

Official Reporter