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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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MICROBIOLOGY DEVICES PANEL

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November 9, 2016
8:00 a.m.

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PANEL MEMBERS:

CATHY A. PETTI, M.D.	Panel Chair
KATHLEEN BEAVIS, M.D.	Panel Member
DAVID WELCH, Ph.D.	Panel Member
CAMILLE KOTTON, M.D.	Panel Member
MICHAEL ISON, M.D.	Panel Member
EMILY BLUMBERG, M.D.	Panel Member
RANDALL HAYDEN, M.D.	Panel Member
MARCUS PEREIRA, M.D.	Panel Member
MICHAEL GREEN, M.D.	Panel Member
DAN MEYER, M.D.	Panel Member
JOANNA SCHAENMAN, M.D., Ph.D.	Panel Member
SUNWEN CHOU, M.D.	Panel Member
RICARDO LA HOZ, M.D.	Panel Member
LINDSEY BADEN, M.D.	Panel Member
DANIEL BRACCO	Industry Representative
ARTHUR FLATAU, Ph.D.	Patient Representative
THOMAS SIMON	Consumer Representative
ADEN ASEFA, M.P.H.	Designated Federal Officer

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JONATHAN NURSE
Director of Government Relations
Infectious Diseases Society of America

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Abbott Laboratories

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M E E T I N G

(8:09 a.m.)

DR. PETTI: Good morning, everyone. Good morning. Happy November 9th. I will call this meeting of the November 9th, 2016 meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee to order. It is now 8:09 a.m.

My name is Dr. Cathy Petti. I am the Chair of this panel. I am a Professor of Medicine and Pathology at the University of South Florida and have expertise in infectious diseases as well as in medical microbiology.

I note for the record that the members present a quorum as required by 21 C.F.R. Part 14. I also add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations regarding the reclassification for quantitative cytomegalovirus (CMV) viral load devices from Class III premarket approval to Class II 510(k) and discuss the appropriate initial classification of quantitative viral load devices for EBV and BK infections in patients immunocompromised due to solid organ or stem cell transplantation.

FDA seeks expert advice to determine the appropriate classification of these assays and to discuss the risks and benefits of quantitative viral load assays to support and guide the development of special controls for analytes determined to be eligible for Class II designation.

Before we begin, I ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. We will start with Dr. Bracco.

MR. BRACCO: Good morning. My name is Dan Bracco. I'm an Industry Rep, and I'm with Roche.

DR. FLATAU: Hi. I'm Arthur Flatau. I'm the Patient Representative. I'm a bone marrow transplant survivor and had CMV post-transplant.

MR. SIMON: I'm Tom Simon from Atlanta, the St. Joseph's Cancer Survivors Network, and I'm a Consumer Representative.

DR. KOTTON: Camille Kotton. I'm the Clinical Director of Transplant Infectious Disease in Immunocompromised Host at the Massachusetts General Hospital, and I'm a transplant infectious disease specialist.

DR. BLUMBERG: Emily Blumberg. I'm the Director of Transplant Infectious Disease at University of Pennsylvania, and I, too, am an adult transplant ID specialist and Professor of Medicine.

DR. HAYDEN: Hi. I'm Randall Hayden. I'm Director of Clinical and Molecular Microbiology and Virology at St. Jude Children's Research Hospital in Memphis, Tennessee, so my focus is on diagnostic microbiology and virology in immunocompromised patients.

DR. PEREIRA: Good morning. I'm Marcus Pereira, adult transplant infectious disease at Columbia University Medical Center.

DR. WELCH: David Welch. I'm a clinical microbiologist from Dallas, Texas. I direct the laboratories of a seven-hospital network that actively measures viral loads, among other routine microbiology.

DR. SCHAENMAN: Good morning. I'm Joanna Schaenman. I'm an assistant professor at UCLA, with a focus on adult transplant infectious diseases and research in immune control of viral infections.

MS. ASEFA: Good morning. My name's Aden Asefa, and I'm the Designated Federal Officer for this meeting.

DR. ISON: My name is Mike Ison. I'm the Director of Transplant Infectious Disease at Northwestern University Feinberg School of Medicine. I'm also Professor of the Division of

Infectious Disease in Organ Transplantation.

DR. BEAVIS: Hi. I'm Kathleen Beavis. I'm at the University of Chicago. I'm a pathologist, the Director of the Microbiology and Immunology Laboratories, as well as the Interim Director of Laboratories.

DR. MEYER: Hi. I'm Dan Meyer, cardiothoracic surgery from Dallas, Texas.

DR. LA HOZ: Good morning. I'm Ricardo La Hoz, and I'm an assistant professor at the University of Texas Southwestern, and I'm an adult transplant infectious disease physician.

DR. CHOU: Sunwen Chou, Professor of Medicine, Infectious Disease, Oregon Health and Science University. I work on CMV genotyping, mainly in relation to drug resistance.

DR. BADEN: Lindsey Baden. I'm at Brigham and Women's Hospital and Dana Farber Cancer Center in Boston and do immunocompromised transplant infectious diseases.

DR. GREEN: I'm Michael Green. I'm at the University of Pittsburgh. I'm a Professor of Pediatrics and Surgery, and I work in transplant and pediatric infectious diseases.

DR. GITTERMAN: I'm Steve Gitterman. I'm the Deputy Director at the Division of Microbiology Devices at CDRH at FDA.

DR. PETTI: Thank you. If you've not already done so, please sign the attendance sheets that are on the tables by the doors. Aden Asefa, the Designated Federal Officer for this meeting, will now make comments and introductory remarks.

MS. ASEFA: Good morning, everyone. I will now read the Conflict of Interest Statement.

The meeting today will include two sessions. The first session is a particular matter of general applicability. The second session is a particular matter involving specific parties.

The Food and Drug Administration is convening today's meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee under the authority of the

Federal Advisory Committee Act of 1972. With the exception of the Industry Rep, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with the Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.D. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to 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 conflict 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. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, during Session 1, the Panel will discuss and make recommendations regarding the reclassification of quantitative cytomegalovirus (CMV) viral load devices from Class III premarket approval to Class II 510(k). During Session 2, the Panel will discuss and make recommendations regarding the appropriate initial classification for qualitative or quantitative viral load devices for Epstein-Barr virus, BK virus, the JC virus, human herpesvirus 6, and adenovirus infections.

Based on the agenda for today's meeting, and all financial interests reported by the Panel members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Joanna Schaenman, Randall Hayden, and Michael Ison.

Dr. Schaenman's waiver addresses her institution's study of an affected firm's related product. The magnitude is between $50,001 and $100,000 for the institution and between $5,001 and $10,000 for Dr. Schaenman.

Dr. Hayden's waiver addresses a related advisory board relationship with an affected firm. The magnitude is between 0 and $5,000.

Dr. Ison's waivers addresses an organization's potential interest in an affected firm and related product, which is imputed to him. The potential magnitude of the organization's interest is estimated in between 0 and $50,000.

The waivers allow these individuals to participate fully in the panel deliberations. FDA's reasons for issuing the waiver are described in the waiver documents, which are posted at the FDA's website. Copies of the waiver may also be obtained by submitting a written request to the Agency Division of Freedom of Information, 5630 Fishers Lane, Rockville, Maryland.

Mr. Daniel Bracco is serving as Industry Representative, acting on behalf of all related industry, and is employed by Roche Diagnostics Corporation.

For the record, the Agency notes that Dr. Linda Cook, who is an invited guest speaker with us today, has acknowledged a financial interest with an affected firm in the form of scientific advisory board services.

We would like to remind members and consultants that if the discussions involve 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 the meeting and will be included as part of the official transcript.

For the duration of the Microbiology Devices Panel meeting on November 9, 2016, Drs. Michael Ison, Lindsey Baden, Michael Green, and Joanna Schaenman have been appointed to serve as Temporary Non-Voting Members, and Dr. Arthur Flatau has been appointed as a Temporary Non-Voting Patient Representative.

For the record, Dr. Ison is a consultant to the Cellular Tissue and Gene Therapy Advisory Committee in the Center for Biologics Evaluation and Research. Drs. Baden and Schaenman are members of and Dr. Green serves as a consultant to the Antimicrobial Drugs Advisory Committee in the Center for Drugs Evaluation and Research. Dr. Flatau is a consultant to the Oncologic Drug Advisory Committee in CDER.

These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered in this meeting.

The appointments were authorized by Dr. Janice Soreth, Acting Associate Commissioner for the Special Medical Programs, on November 8th, 2016.

Dr. Cathy Petti, who is a voting member of the Panel, will serve as the Chairperson for the duration of today's meeting. Thank you.

Before I turn back -- turn the meeting back over to Dr. Petti, I would like to make a few general announcements.

DR. GREEN: Can I make a clarification, please? I'm not a consultant to the Antimicrobial Committee. I'm a full member of the Antimicrobial Committee.

MS. ASEFA: Oh, okay. Thank you.

Transcripts of today's meeting will be available at the Free State Court Reporting, Incorporated.

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

The press contact for today's meeting is Stephanie Caccomo.

I would like to remind everyone that the 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 Artair Mallett at the registration table.

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

And a few additional announcements. There's a lunch menu for the Panelists on top of your folder. If you could fill that lunch menu out and return to Artair Mallett at the front desk, that'd be great. Also, please consult him for transportation needs when you leave. And if you have any issues with the temperature of the room, please e-mail him as well.

Finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

Dr. Petti.

DR. PETTI: Thank you.

I now introduce Dr. Uwe Scherf, Division Director of the Division of Microbiology Devices at the FDA, who will provide a short welcome and introduction.

DR. SCHERF: Yeah, good morning. My name is Uwe Scherf. I'm the Division Director in the Division of Microbiology Devices, and just some additional few housekeeping announcements.

The restrooms, if you exit this room here, are to the left.

Regarding the lunch, you already heard you will be taken care of. The attendees, you can enjoy the opportunities here in the hotel, or there are also nearby restaurants as well. And during the breaks, the breaks are announced, and coffee will be available outside for your enjoyment.

So what I would like to do is to welcome all of you to Washington, the Panel members, the speakers, and the attendees to this CDRH Panel meeting, which is very important to us.

I would also like to thank the speakers and the Panel members for their public service. Your contribution to a Panel meeting like this is a clear public service, and I would really like to thank you for that contribution, because for us, it's very important to get your input and get your feedback for our decision making.

Panel meetings like this represent an important part of FDA's deliberation as we move forward with some of our decisions that are related to submissions as well as evaluations of certain reviews. Please recognize, we make your advice part of our decision, and we really appreciate all the discussion that you will have today and the feedback that you will provide us.

As you know, the FDA has missions, and the most known one is to protect public health. We do this mostly by reviewing devices before they go to the market, in the premarket environment, as well as after they have been introduced into the market, the postmarket environment. But there is also a second mission that we have, and that is actually to promote public health. And we work very hard to accomplish that as well. And I

have to say that today's meeting is more on the mission side of promoting public health.

We are contemplating, as it was said before, the appropriate classification of quantitative viral load assays for transplant-associated opportunistic infections. And we believe now it is time to actually have some benefit with discussions, and have some discussions on how we could identify, how we could mitigate the identified risk to appropriately move forward.

So today's meeting's goal, we have three. We would like to hear some open discussion on the reclassification of quantitative CMV viral load assays, currently Class III into Class II. We would also like to obtain the Panel's recommendation regarding the appropriate initial classification of EBV and BK virus-related infections. And lastly, we would also like to hear some discussion of what would be the appropriate special controls that would allow us, the FDA, to appropriately address some of the designation that fall into Class II designations.

We have an outstanding and tight agenda today. And I would sincerely thank the Panel meeting's team who put this together, especially Aden, Kristy, Parker, Beena, Silke, Pat, Ines, Li, Steve Lovell, and Steve Gitterman. Thank you all for your hard work in putting this together. This is an excellent agenda and meeting so far today.

The morning will be reserved for the discussion regarding the reclassification. You will hear background of CMV regulation or path and intended uses by Dr. Gitterman, followed by two presentations from experts in the field. Dr. Limaye will present on the clinical aspects of viral load testing for CMV. He is from the University of Washington. Dr. Cook will then -- also from the University of Washington -- go into the technical issue of CMV viral load assays and the CMV standards. These talks are followed by a FDA presentation by Dr. Whitaker, and she will share with you the FDA perspective on the CMV viral classification.

All of that is followed by the Open Public Hearing, your panel deliberation, and then also the questions to the Panel.

Then the remaining day, we'll be addressing and we'll discuss the benefits and risks of assays like EBV and BK as models for opportunistic transplant-associated viral infection. The agenda is similar to the morning: Introduction and background by Dr. Gitterman. Then we have again the clinical aspects of EBV by Dr. Limaye and the laboratory aspects by Dr. Cook.

And again, we will have Open Public Hearing, the Panel deliberation by the Panel, as well as then the questions to the Panel.

That concludes my introduction, and I would like to thank you again for your service, the speakers and the Panel members, and I put the floor back to the Chair of the Committee, Dr. Petti.

Thank you very much.

DR. PETTI: Thank you, Dr. Scherf, for that introduction.

Next, I introduce Dr. Steve Gitterman, Deputy Division Director of the Division of Microbiology Devices at the FDA, who will provide a background of CMV regulatory path and intended uses.

DR. GITTERMAN: Thank you, Dr. Petti. I will try and move at a blistering pace and get us back on. It's always never good when you're behind and it's only 8:30 in the morning.

Okay. Why are we here? What is the purpose of the meeting? And the purpose of the meeting is to address whether CMV viral load assays, which are now Currently Class III -- and you're going to hear more, very specific information about Class III by Dr. Whitaker, so I'm not going to repeat it at this point in time, but the question is can they be reclassified or downclassified, since Class III is the highest class, to a Class II, which is a 510(k). And we will

talk a little bit about what the risks and benefits of that are and what that means.

But the question I'm sure that people are asking right off the bat was why are these Class III to begin with? And it really sort of is straightforward. You don't have to read this, but this is the definition of what FDA looks at in -- when they -- excuse me, first approved cytomegalovirus. And it's an in vitro nucleic acid-based assay, using real-time PCR for the quantitative measurement of CMV DNA.

That sounds so straightforward. But again, at the time these assays were first being developed, it wasn't straightforward. And I'm sure around the table are people who remember, it would have taken a room this size to be doing -- well, maybe not this size but, you know, a tremendous amount of staff and expertise to be doing these accurately.

Looking at it through the eyes of 2016 is very different than looking at it, you know, back when the first test was approved. And even though the first tests were approved in 2012, the development was far longer on it. Again, I'm bringing coals to Newcastle when I say that.

The original intended use, as everyone is aware, it was an aid in the management of solid organ transplants who were undergoing anti-CMV therapy. And again, that's relatively narrow, in certain respects. People know what -- you know, the way it's used now, but at that point, that was what the data submitted to FDA clearly supported.

And the reason we can say that is that, at the time, there was a demonstration of clinical effectiveness. And they did show that the test was informative in the setting of solid organ transplants on patients who were treated with ganciclovir or valganciclovir because the data was taken from the VICTOR study. All this, I'm sure, is second nature to everyone here. But again, that was still relatively new at that point.

Now, what is important for just one -- this was solid organ transplants. The intended use remained for that. That was the original intended use. The analytical studies, at the

time of the first approval, did include measures against the WHO standard, but again, that was late to the game, and that was not in the early development. That's a fairly recent development.

As people are aware, the data's available from the VICTOR study. And this was the identical data for the sponsor, for the drug sponsor, who also happened to be the device sponsor. That's usually not the case. And having that amount of data, a lot of times, doesn't exist. One could consider establishing clinical effectiveness a challenge to sponsors who, in fact, don't have that information available.

The study evaluating -- there was a study, the VICTOR study, which established the clinical effectiveness of the device for the proposed intended use, as well as showing a threshold level at which it appeared risk was different just with negative viral load. The patient risk, at that time, was believed to warrant classification as Class III.

And I think, again, times change. But before there's a tremendous -- and again, we're talking not very recently, but there was a time it took quite a bit of expertise to be using ganciclovir, or valganciclovir wasn't available. This can be a fatal disease. Even with the use of viral load measurements, it can be a fatal disease. And we also won't -- you know, there's a great relationship, even outside of direct CMV disease. There's a relationship to organ, you know, immunosuppression, organ loss, etc..

You know, even though, again, experts like yourselves, and perhaps even the general infectious diseases community, is much, much more comfortable with these patients, we can't -- recognize that this was the primary -- you know, a tremendous reason for both graft loss and loss of life, you know, so to speak, back in the day.

And again, Dr. Whitaker will again, very, in some depth, discuss the difference between Class III and Class II and what the reasoning is or what the strict definition of Class III and why at that time it was clearly felt to warrant Class III status.

Now, why consider reclassification? We'd all agree there's tremendously more information available about the use of viral load in transplant patients. It's a different era. And, of course, there's much more information available about the use with both approved assays and non-approved assays.

I think, and I certainly would be -- I think we'd all be glad to hear alternative opinions, although I'd suggest arguing with Dr. Limaye that the clinical effectiveness of viral management of viral load measurements in transplantation is unequivocally established. I don't think anybody's going to do a randomized controlled study of viral load testing.

There's reduced assay variability across assays. Now, I'm going to say that with caveats, and several people in the room were involved in those studies, looking early on, in the absence of a standard, how tests did against a sort of consensus sample that was sent out to various labs.

There's an -- now, this is very important, and that's why it's italicized. You know, we're just not doing this to generate work for ourselves. Not only do we try and do what's in the best interest of patients and promoting public health, is what Dr. Scherf had said, but we have a regulatory mandate to be least burdensome and to appropriately classify devices. It is not our goal to keep something out there as a Class III device if it shouldn't be. So this is our regulatory mission, and that's, you know, perhaps a major reason why we're considering reclassification.

However, and all this will come up, there are significant differences in the regulatory overlap, oversight between a Class III and a Class II device. And despite what I've just said, despite more information, despite clinical effectiveness being there, there still are good reasons why somebody could cogently argue that perhaps it should be Class III.

Lowered barriers -- and this is another way of saying the same thing, but being a Class II, and I think it will come up later, that may pose lower, less challenges -- barrier is

not a very good word, less challenges to other manufacturers, other sponsors, having their -- sending their tests in for FDA approval, or at that point, if it's reclassified, FDA clearance, and that has risks.

And again, I've said this probably four times, but it still remains a very high risk disease, despite the fact that a lot of people feel far more comfortable with it, and the fact that -- of course, around the table everybody has great familiarity with it -- it is a high-risk disease, and the risks of inaccurate results are fairly dramatic.

And the last thing I would say is there still remain clinical issues to be resolved. And I'd say that's true with all viral load assays. Even though we think we know everything about it, we often don't and often think to things like HIV, even though assays have been around for a long time, we still have questions about blips, questions about what to do at the low end, how to treat patients. So it's not as if everything to be known is known at this point.

So what's going to happen? At this point, I cannot thank enough Dr. Limaye and Dr. Cook for journeying here from the University of Washington for these presentations. I have been able to glance at their slides, and you know, we couldn't ask for two better presentations. You could correct me if I'm wrong, later.

There will be the FDA presentation by Dr. Whitaker.

I'm raising the bar for you guys, but it's okay.

There will be an Open Public Hearing. We, of course, would welcome comments because there are a lot of people who have skin in this game.

And again, we especially thank the Patient Representative and the Consumer Representatives for their weigh-in.

And there will be Committee discussion. So again, to reiterate what everybody has said, thank you very much.

And Dr. Petti.

DR. PETTI: Thank you, Dr. Gitterman, for the presentation.

Does anyone on the Panel have a brief clarifying question for Dr. Gitterman?

(No response.)

DR. GITTERMAN: Thank you.

DR. PETTI: Well done.

Next, I introduce Dr. Ajit Limaye of the University of Washington, who will present the clinical aspects of viral load testing for CMV.

DR. LIMAYE: All right. Thank you, Dr. Petti and Committee members, for the invitation to be here. I've very much enjoyed the slightly warmer rain than in Seattle the morning after.

My task, over the next 15 to 20 minutes that Dr. Gitterman has asked me to cover, is really to provide clinical context and background for the discussion about reclassification of CMV assays and their use in transplantation.

Implicit or inherent in this discussion are really certain assumptions and concerns that ultimately might prove to be correct or might prove to be incorrect. And I think Dr. Gitterman has already provided some background that ultimately reclassification of these assays might lead to a lower barrier, or maybe a better term is appropriate here, challenge, to having assays that ultimately undergo FDA approval or clearance, and that more commercial assays will eventually, potentially become available if this were to happen, particularly with what's happening with laboratory-developed tests.

And we know from data that people are well aware that the more the number of assay platforms and individual components of assays, the greater variability that is, that will be a consequence of that route. And ultimately, the concern here, is that this could have a potential negative impact in that the assays that are now available, greater assays, greater

availability, that the assays may not, in fact, be able to support their intended purposes in transplantation.

I think it's important to balance these concerns about what might happen with the current situation, which is that there are multiple laboratory-developed tests that are available, that have been widely, variably evaluated, and some perhaps far less rigorously than one would hope, and in fact, that even a classification at a Level II might allow for greater consistency in the evaluation of assays than might presently be the case with multiple assays available with variable evaluations.

So really, providing the background about CMV, I feel a little funny doing that when the panel is full of transplant infectious disease experts, but I'll review with you very briefly just the background about CMV, provide what I think are evidence-guided recommendations about how and where these assays are used in transplantation, really to frame the discussion for subsequent speakers and Dr. Cook to go over in more detail some of the more complex issues related to the specifics of these assays.

So CMV, as has already been mentioned, has a major negative impact on transplantation, and really, the focus, I think, for viral load assays really relates to the impact that CMV has in terms of direct morbidity and mortality related to CMV, because ultimately, those are the clinical manifestations of CMV that have been most closely linked with viral load.

There are probably a number of other important biologic effects of CMV that occur in transplantation, but the actual relationship of those biological effects to viral load, I think, have not been as clearly established as they have been for the direct morbidity and mortality mediated through CMV disease.

The risk factors for CMV disease have been reasonably well defined in the major transplant settings of hematopoietic cell transplantation and in solid organ transplant

recipients as well. There are some differences but many parallels, with intensity of immunosuppression being one of the major risk factors for development of CMV-related complications.

We know that CMV viral load assays are extremely widely used and really are part of the clinical practice fabric, if you will, of transplant infectious disease, and the use of these assays in a number of different indications or uses have been incorporated into major guidelines for the prevention and treatment of CMV in transplantation. And I think it's important, that as we have this discussion about blood viral load assays, the field has already evolved and moved on to other indications that may have an impact on the discussion about reclassification.

And an example for that would be that many laboratories are now using these assays, which were initially developed specifically for blood quantitative viral load measurement, into site-specific assays, for example, as an adjunct to the diagnosis of CMV pneumonia by analyzing bronchoalveolar lavage fluid, in CSF for diagnosing CSF, central nervous system CMV infections.

And at least for now, I think it's reasonable to say that the majority of clinicians recognize that there are important limitations of viral load quantitation, and at least there are some safeguards, you could say, with regard to the use of these assays.

First, these assays are not used completely in isolation. They're certainly used in the context of other available clinical information, laboratory information, and frankly, if the assays yield a result that seems completely out of context with the rest of the clinical scenario, they are repeated. And so there are some safeguards with regard to those strategies, to make sure that viral load assay results are in line with the rest of the clinical picture.

And I think, as assays have been around, we have a greater comfort level and

understanding that serial testing often provides greater information than a single viral load in time. And, in fact, there's reasonable data in multivariable analyses suggesting that the rate of increase in CMV viral load over time has an important predictive value for subsequent CMV disease.

So the fundamental principles underlying the use of CMV viral load assays in transplantation are summarized here and should be well familiar to everyone in this room. We know that the absolute viral load in blood is a reasonable, but not perfect, predictor of subsequent disease risk, or having CMV disease at the time of the viral load. That relationship is not perfect, and I'll provide some specific examples on context where that is not the case.

We know that the rate of increase in the blood viral load also independently seems to add additional information about the risk of subsequent development of CMV. So in addition to the static components of the assay, a single measurement in time, we know that certain aspects, in terms of viral kinetics, provide additional information.

And then Paul Griffiths and Vince Emery have done work suggesting that there's not a linear relationship between the blood viral load and risk of CMV disease, and have hypothesized that there may actually be a threshold above which increases in viral load substantially increase the risk, whereas below that threshold, increases in viral load have less of an impact and subsequent risk.

So what are the major uses or clinical indications for CMV viral load measurement in transplantation? The first, which really is unique to the setting of solid organ transplantation, because this entity, clinical entity of CMV syndrome is simply not recognized as a clinical entity outside the solid organ transplant setting, is the diagnosis of this clinical entity called CMV syndrome, primarily seen in the context of primary CMV infection.

The second important clinical indication is as an adjunct to the diagnosis of end-organ CMV disease. There are some important caveats, and in fact, the recent guidelines that were just published within the last couple of weeks have significantly de-emphasized the contribution of blood viral load towards making a definitive or probable diagnosis of CMV end organ disease, and I'll review those data with you.

There are two major strategies for CMV prevention, and at the home -- one of the major needs for preemptive therapy, which is providing antiviral therapy based on viral load kinetics and viral loads, is really fundamentally based on having a very sensitive marker for early CMV replication, and that strategy is used primarily in stem cell transplantation, although there are indications in solid organ transplant as well, and then finally, monitoring response to therapy.

So we're going to have a detailed discussion about the nitty-gritties of viral load assays and assay characteristics, but simply and perhaps simplistically, as a clinician, what matters to me and my colleagues in thinking about, what does this CMV viral load assay result mean, I've just sort of framed a few questions that I would have from my laboratory, Dr. Cook, about what the assay results mean.

And one of them is just a simple question. If my patient -- if I think my patient has CMV disease, is this assay that you're using likely to be sensitive enough to detect a meaningful viral load such that I wouldn't falsely think that his CMV disease is due to something else? So it's really getting at the issue of whether the assay has the requisite sensitivity that ultimately would be linked to some clinical illness.

Since a majority of viral load assays are used for monitoring changes in viral load over time, a fundamental question that clinicians would have about these assays are is this change when I monitor the viral load now, have some intervention, I'll monitor the patient later and I get a different result, are these two results truly different? And are those two

values truly different, whether I'm looking at a person whose viral load is 100 or 500 versus 500,000?

I think that's a very important and common question that comes up with viral load assays. And we can redefine these into far more precise terms, that Dr. Cook will do, in terms of what these mean in evaluating an assay. But as a clinician, you just want to know, are these two values really different, or can I explain it away based on variability in the assay, and importantly, over a very large range of viral loads that we clinically deal with.

And then finally, probably the most difficult question to answer, because there probably is no single answer that is universally applicable across transplant populations, is what's a clinically significant number? Should I get excited about this number, or is this number, oh we see this, we see this in healthy people, we see this in transplant patients who are healthy? Those are very difficult questions to answer, but it is one that would be very important for clinicians to have at least some handle on and at least have some context in terms of what the assay result might be in people who didn't have a transplant or who had a transplant but are not sick.

So one of the major indications is the diagnosis, or is a diagnosis of CMV syndrome, which I alluded to earlier. It really only applies to solid organ transplant patients because the syndrome is not defined as a clinical entity outside of solid organ transplant recipients. And in recent definitions, they essentially chose to remove the category of proven CMV syndrome because the contention was that it was just simply impossible to exclude other herpesviruses, other viral causes that could produce an entirely similar clinical syndrome, or clinical illness, I should say.

They did not define a category of possible but rather said that CMV syndrome was something that, practically speaking, could only be called as a probable diagnosis and required the detection of CMV in blood, combined with various clinical and laboratory

abnormalities. And there's a number of issues and challenges when thinking about the use of viral load assays in this clinical context.

First of all, there is no specific defined viral threshold for clinical significance, and as I alluded to earlier, it probably varies according to patient population. We know, and Dr. Cook will talk in great detail, about the variability in the sensitivity of assays, but if my assay were to be very, very sensitive, I might diagnose three times as many patients with clinical CMV syndrome than somebody else whose assay is much less sensitive, even if they have the same other laboratory and clinical abnormalities, which are fairly nonspecific in the solid organ transplant setting.

Ultimately, we don't really know what, precisely, all assays measure. And I think the bigger question is would different things measured have a better predictive capability for the things that we try and diagnose, in terms of clinical entities, and Dr. Cook hopefully will address that a bit in her talk. And then finally, this issue about having only a probable rather than a proven category of CMV syndrome is based on the well-documented presence of multiple other pathogens that could present in the same way as CMV syndrome.

The second major clinical use of CMV viral load assays is as an adjunct to the diagnosis of end-organ CMV disease. And here, I think there's been a major shift in the recently published, within the last couple of weeks, definitions of CMV in the reference that's shown there, in that demonstration of CMV in blood in a patient who's suspected to have end-organ disease is really no longer required or doesn't really help you get to a higher level of confidence in the diagnosis of CMV end-organ disease. And overall, the definitions vary slightly depending on gastrointestinal disease versus pneumonia versus some of the other clinical entities.

But conceptually, to have proven or probable disease requires the presence of clinical symptoms and demonstration of CMV, specifically at the site of suspected

end-organ disease, by one or a number of methods that are listed here.

And what was intriguing was the inclusion in their definitions that perhaps in the future, there could be a possible category in which quantitative PCR could be applied directly to specimens from the site of interest as a way to reach a diagnosis of possible CMV disease, which I thought was interesting.

Limitations and other issues that we should consider when thinking about the use of CMV viral load assays for end-organ disease relate to both non-biological, assay-related issues that Dr. Cook will cover, and I'll just ignore it here for the sake of expedience and focus on some of the biological issues that impact or that present challenges when using CMV assays for this intended purpose.

There is the issue of compartmental CMV replication, which has been not necessarily reflected in the blood viral load. We have excellent examples, and there is some recent data suggesting that up to 40 to 60% of certain populations of solid organ transplant patients who have histopathologically proven CMV gastrointestinal disease do not have concurrent viremia, even with very sensitive tests.

So that has important implications when evaluating a patient with suspected gastrointestinal disease, what the negative predictive value, for example, might be of blood viral loads. And so those are important to consider. And some of the others, there are also examples where the same issue of compartmental replication probably impacts the sensitivity and specificity of assays in this clinical setting. And then finally, there is no absolute threshold above which or below which we can be comfortable that the patient does not have CMV end-organ disease.

The third very important clinical use of viral load assays relates to serving as a marker to guide preemptive therapy, which is one of the two major strategies for CMV prevention, that is recommended, accepted, has a body of evidence to support its use, both

in the setting of stem cell transplantation, where it tends to be the primary method or approach to CMV prevention, and then also in solid organ transplant, although there may be a greater use of prophylaxis in that setting.

And here, the approach is that no antiviral drug is given at the outset, but rather, patients are monitored intensively during the period of risk. When evidence of CMV viremia is present, antiviral drug is administered. The patient is treated until viremia clears. Monitoring is reinstituted. And this approach is thought to lead to a lower incidence of late-onset CMV disease, although there's great controversy about which of the two approaches might ultimately have greater benefits rather than disadvantages.

The importance of CMV viral load assay characteristics is highlighted here. Ultimately, if we were to have assays that are approved, what sort of criteria would it be important that those assays possess?

This is "How I Treat CMV Disease," by two experts in the field, Per Ljungman at Karolinska and Michael Boeckh at Fred Hutchinson. And here I just want to point out the fact that in this approach for preemptive therapy, the viral -- the initiation of preemptive therapy is based on both absolute viral load -- and you can see that these viral thresholds are quite different based on the risk of CMV disease based on patient factors, and then importantly, in addition to the absolute viral load, even at relatively low ends of the assay, there is also a premium placed on viral kinetics, such that even below the thresholds that are required to initiate preemptive therapy, relatively small changes in the viral load are used as triggers to initiate preemptive therapy.

And so in thinking about assays and what characteristics are relevant for the indications that they're used for, these are the things that I think it would be important, at least from a clinical perspective, to feel confident that this assay would do what I'm asking it to do, for purposes such as preemptive therapy.

And finally, there is the use of viral load assays for monitoring response to therapy. And we have good data from a randomized controlled trial of a fairly large cohort of patients, and so we have some background with which to interpret whether a patient is responding appropriately to therapy or not. And we have both clinical parameters, in terms of when we would expect to have clinical improvement. We also have virologic parameters of expected reductions in viral load in patients who ultimately had their clinical infection treated appropriately. And a viral load reduction within 2 weeks has been used as, at least, a trigger for deciding when to even do resistance testing.

In addition to clinical and virologic response, there are good data to suggest that individualizing therapy and treating until viremia has completely cleared would be an important endpoint for therapy to hopefully reduce the risk of a relapse, which is an important clinical problem.

But again, thinking about what you would want your assay to do, viremia -- the sensitivity of the assay could significantly impact on whether or not one would have therapy stopped, or whether therapy might continue longer if the assay is significantly more sensitive.

In terms of monitoring response to therapy, resistance is obviously a very important concern, and we know that alternatives to ganciclovir are very, very toxic. And we have important limitations of current genotypic resistance assays in terms of turnaround time, variable reporting, and these are relatively expensive. So we really rely on changes in viral load to help us determine, make those difficult decisions about whether to send resistance testing, or in some cases, whether to switch empirically, without laboratory confirmation, to more toxic therapy.

And then finally, I mention this issue that assays in clinical practice are already evolving to use site-specific testing, and it adds yet another layer of complexity and another

variable that we should keep in mind as we evaluate these assays.

So the current status is that there are major issues with across-lab comparisons, which Dr. Cook will address. I think, in general, transplant physicians are aware of this issue, but it definitely complicates clinical care. And I would just say, as a clinician with some laboratory background, that clinicians have relatively little input into laboratory assays. And just because we work at a fine institution that does a lot of transplants, we presume that our assay does what it's supposed to do or what we use the assay to do.

And, in fact, in general, the amount of data that's fed back to clinicians about the assay is relatively little, and we often don't know exactly how the assay performs for the specific intended purposes for which the assay is used, particularly with regard to sensitivity and what changes in viral load are clinically significant, and then ultimately, some of the important clinical links to that laboratory information.

So the potential outcomes of reclassification, I think there are some potential good outcomes that could result. Ultimately, there would be fewer challenges. There might be more assays. Ultimately, might they become less expensive? There might be more availability to perform these assays in real time, shorter turnaround time, and use them for on-site testing rather than referral lab testing.

I think one of the major Achilles' heels to preemptive therapy is the availability of rapid turnaround time with accurate viral load assays, and this theoretically could address that important limitation and might potentially lead to greater use of preemptive therapy rather than exposing a larger proportion of drugs to -- larger proportion of patients to expensive and potentially toxic drugs.

But there are also concerns obviously. In the end, if assays are deemed to have lower quality and less appropriate controls are in place, variability in the sensitivity in the assays could lead to lack of recognition of patients who are at increased risk and could be a

major issue when using preemptive therapy. We might not treat patients for the appropriate duration of therapy, based on insensitivity of the assay, for example, or overtreat patients if the assay is detecting what might be detected in healthy seropositive patients, for example.

Inadequate quantitation could potentially lead to either over- or underdiagnosis of resistance, and even potentially lead to inappropriate changes, empiric changes towards more toxic antiviral therapy while we're waiting for genotypic test results.

So those are some of the thoughts that I would leave you with.

And Dr. Cook, please.

DR. PETTI: Thank you, Dr. Limaye.

Next speaker, I'd like to introduce Dr. Linda Cook of the University of Washington, who will present the technical issues with CMV viral load testing and standards.

DR. COOK: Good morning. It's nice to be here, I think.

I have been charged with talking about the technical aspects of what goes on with CMV testing. I'm going to spend the first part of the time talking about just basically how we do a PCR assay and some of the technical things that we need to know about it.

So the first part of this is really not going to be that specific for CMV. And we'll cover all the viruses that we're going to talk about today. And then the second part of this presentation's going to talk about what we know about CMV standardization and assay comparabilities.

So I'm going to start with some very basic things. For those of you who stayed all night, up all night listening to the election results, and you're familiar with this stuff, you can take a 10-minute nap here. But for the rest of us, essentially, all PCR assays that we're talking about today consist of two steps. One is the DNA extraction, and one is real-time PCR amplification.

Why do we do extractions? Because most of the things that are present in the sample, in addition to the DNA or RNA itself, inhibit the PCR reaction. So it's important for us first to purify DNA, in this case for CMV DNA, and then we can do the second part of the assay.

So what about extraction is important that we need to understand, as it relates to the controls we might build into the system? So there are a variety of methods. We've mostly gone from old precipitation methods to newer methods. The first step, almost in every case, is lysis. We're looking to get rid of the cell membranes. We're trying to get rid of all the proteins. We're trying to just mix everything all up and try to then be able to purify the DNA.

So how do we that? We bind the DNA to some sort of solid support. Generally, there are two methods right now, something called a spin column, which is a little centrifuge tube that has a filter in the middle of it, and the filter is coated with silica. So we take that gemisch of everything we've made and spin it through the column. The DNA binds to the column.

If we're using automated instruments, these days we use silica-coated magnetic beads, and the instrument basically uses magnets to do that purification for us with almost all of the automated instrumentation using those silica-coated beads these days.

After we get the stuff bound, the DNA bound to the solid support, we wash it a bunch of times, and then we elute it by changing the buffers, so fairly simple.

And what do we worry about when we're looking for the evaluation for an extraction method? We worry about yield. We worry about cross-contamination. And we worry about linearity of the yield.

So, in virology, in contrast to when we're doing something like genetics testing, we usually only can measure the amount of virus that's there by doing a PCR assay. So it's hard

to evaluate just to the extraction by itself. We have to usually look at both the PCR and the extraction steps together. There are a few methods right now that combine the two steps together, and so you really can only evaluate it at the end of both methods.

The methods have changed and improved so much that what I would say would be that for these large DNA viruses, the extraction's probably not a major variable at this point. Most vendors make similar types of extractions, and maybe two or fourfold is about the limit of the difference that you see from different commercial extraction instruments, so something you need to keep track of, keep in mind, but probably not a major variable at this point.

So here's an example of the kinds of extraction yields that you can look at. On the left-hand side is actually an earlier version of -- from a paper that actually looked at the quantity of DNA out of samples that were whole cells, and that the different bars there are just different extraction methods. So you can see, for various samples, they agree pretty well.

On the right-hand side, at the bottom, are colored markers from some data that we presented a few years ago. These were four different extraction methods. You can see, again, pretty good consistency across different methods. The one on the right-hand side of that, that's the orange and green color, that's actually an RNA virus, a little more variable for RNA than for DNA, but for the most part, pretty good extractions. And you can measure it, as I said, either by looking at sort of the chemical OD, for example, versus the amount of virus that's actually there, so fairly simple to evaluate yields.

One of the issues about extractions is that, of course, you want to do a whole bunch of different sample types, as Ajit alluded to. Mostly we know about plasma and whole blood, not so much about spinal fluid, dried blood spots, urine. It's not nearly as much tested or studied in those situations, but a lot of argument about whether plasma or whole

blood is the correct sample.

Another thing that we do when we're looking at yields, particularly for automatic extraction instruments, is we do something that in the sort of lab jargon is called a checkerboard. So we do a very high positive sample right next to a negative one, and then another high one and a negative one. And what we expect -- and I have no idea why it's flashing like that. I apologize. But we want all the white squares, the ones that are negative, to be completely negative regardless of how positive the one next to it is. And that's pretty much an absolute given for all of our extraction instruments. And then when we set the PCR up, we want the same thing to happen in that case, but these examples are usually used as part of the extractions.

So that's all I'm really going to say about the extraction part of it. For the PCR part of it, what are the things that we need to do, and what are the tools that we need in order to be able to see whether or not a PCR assay is working correctly?

So, first, I've just thrown up a small slide here, tried to keep it really simple to get the basic idea, which is we're looking at double-stranded DNA. What we do first is to heat it up so that the two strands separate as in this picture. They're no longer annealed to each other. And we throw primers in. Primers are 20 to 25 bases usually. They are exact matches to the area of the sequence we're trying to amplify. And we put DNA polymerase in there and make a copy of it.

On this picture, there is something there called reporter and quencher. That's a diagrammatic representation for one of the early probes that we used. The probes are fluorescently tagged. There are probably more than 15 different ways now that you can put this fluorescent color onto these amplicons as you do it. And some of them go directly onto the primer. Some of them go onto the end of the amplicon. A variety of different kind of ways that you can do that, but that is hence the reason why we call this real-time PCR. It

means that we're looking at the accumulation of that particular product over time by monitoring the fluorescent tag that will bind onto that particular marker.

So how do we do that? Each one of these is an individual PCR reaction. On the left-hand side of the screen shows you all the things that go into this PCR reaction. The way we do this is much simpler than it used to be. We basically mostly buy premade mixes at this point. And -- but it is really very complicated chemistry, and all those things have to be in the correct combinations and concentrations in order for it to work right.

On the right-hand side is just a typical picture of what we talk about for PCR, to just remind you that this is logarithmic amplification, 1, 2, 4, 8, 16, 32, as we cycle from melting everything to copying, to melting and copying.

So how do we monitor this? This is an example. A lot of times we're using 96 well plates or a strip of 8 or a variety of combinations. And this is what you get out of monitoring, with some sort of optical device, the amount of fluorescence that happens over time as you do the amplification reaction.

So on the left-hand side, at the bottom, you start with very little fluorescence, essentially background fluorescence, and as you cycle, you finally get to the point where you accumulate enough amplicon that you begin to be able to see it. And as you do that, each time you cycle, you should get twice as much as you had the time before. So you're having essentially logarithmic amplification, which gives you that nice steep curve. And then after you kind of run out of everything, you get to that non-exponential part at the end, which is in the upper right-hand corner of this graph.

So the most useful part of this assay is the part right there that's labeled the C_q value, in other words, the crossing cycle value, the number of cycles that it takes you to be able to see the product. And that number of cycles is directly related to how much material there was there in the first place.

So when we're doing this particular kind of assay, what do we want to do? So here's a picture of a bunch of individual amplification reactions. And for a given sample, we want the efficiency to be 100%. At every cycle, we're getting an exact duplication of twice as much. And so in order to do that, we control the conditions such that we push those amplification reactions to be as straight up and down as possible, and as far to the left as possible, which means we're maximizing the assay efficiency and getting the maximum amount of signal out of that particular sample.

So how do we figure out, for a given assay, how efficient it is, how good is it at complete copying at each individual cycle? What we do is we take serial dilutions -- in this case, these are 10-fold dilutions, and we run them all, each in an individual well, and then we look at the cycle threshold for each one of them, and so we can calculate a linear regression slope for that particular set of results. And this is the way we normally do a standard curve.

So almost all of our real-time instruments can plug this in and give us the result for that, give us the slope and a regression line.

So how does that work? It's basically diagrammatically represented like this: You start with one copy; then you go to 2, 4, 8, 16. You can draw that on a graph in the lower right-hand corner and calculate the slope. A 10-fold increase would be expected to be about 3.3 cycles.

So here is how we measure efficiency. There are different formulas used, depending on what instrument you're using from which manufacturer. And here are just three different ways to calculate efficiency. One of them is to look at the slope itself. Another one is to use that slope in a calculation to determine a range, which we would hope would be 100% or another vendor uses 2 as that number. So a range in that case might be like from 1.8 to 2.02.

So there are a number of ways in which one can express this efficiency calculation, and like I said, we're trying to get it as close to 100%, or 3.3 or 2, depending on how we do the calculations.

So why do we care about that? What difference does it make? Here is a graph from a poster that was presented at a meeting not too long ago, and basically what this shows is the black line is 100% efficiency, the gray line is 80% efficiency. And the authors calculate that if you have a 5% difference efficiency at 25 cycles -- 25 is somewhere around maybe 100,000 for most of us, that you're going to be about 5% off. But by the time you get to the end, around 30 or 35 cycles, which is where we're talking mostly for our assay sensitivities of 100, 200, or 300 copies, that you can be as much as 2 logs off. So it's very important that we have 100% efficiency or as close to it in all of our assays. If not, we get less efficiency overall and definitely impact the bottom of our curves.

So a second way that we can check on our PCR assay efficiency and the fact that each individual well is working is based on the idea that most of the samples that we run are actually negative at the end. And so, to make us feel better that the assay is actually working and we did everything correctly, and to ensure that each well is good, we run an internal control.

So this is a completely unrelated piece of DNA we throw in the mix. We also throw primers and probes in there. We usually add this at the beginning of the extraction, so we're controlling both the extraction and the PCR. And the master mix, we put in primers and probes that will amplify this as well.

So we usually keep this at a low concentration, so it's a good test for the bottom end for our most efficient assays. And the graph down there at the bottom is a slightly different plot that shows the amount of color that's coming out of four different things that we're monitoring. In this case, the virus amplicon is the blue one. And the green one down there,

which you see amplification that amplifies around cycle 34, is our internal control. So when we look at a sample like this, we can say yes, everything in there was right. The master mix was performing well. The efficiency was good. We just didn't get any virus.

All right. So some of the parameters that we might care about in relationship to this assay also are linearity. So we want the assay, as Ajit said, to be extremely accurate, from the very top to the very bottom of our assay. So we have to worry about linearity for multiple logs. This is very different from most laboratory tests where you might get a log or two. We want to have good assay sensitivity, good linearity from the top to the bottom of an assay. So we're going to pay attention to every component and make it as linear as we can at the top and at the bottom.

So here's just an example of a couple of different curves that you might have. If it's nonlinear at the top, you don't have enough reagents. There's some other reasons it could not be linear at the top. That would be an example of what's there with the green line. And for the bottom, nonlinearity might be a function of you don't have quite enough primer or probes or something wrong with your extraction. So we would want, on a regular basis, to check each of our assays as we set them up, to make sure that they're linear throughout the entire measuring range.

All right, so what about sensitivity? This is probably the hardest thing to talk about and one that is conceptually a little bit more difficult to understand. And I try to describe it as assay sensitivity is a function both of linearity and probability. So it's possible, by PCR, to detect to one virus in a cell -- in a well, sorry. But can you get the virus in the well so that you can measure it?

So the example that I would give you that we read out all of our results as something per mL. But in reality, we only start with 200 µL of that mL. And then when we elute the concentration from our extraction, we essentially elute in half the volume. So whatever

was in the immediate stuff, we concentrated it by twofold. And now we have 100 µL, but we only use 10% of it. So if you're keeping track, we're using much less than 5% of the original volume.

So what difference does that make? So on the left-hand side is an example. If you've got a high quantity or a fairly high quantity, you start with 5,000 copies. You have it concentrated a little bit, and you're ultimately putting 500 copies into the PCR assay, which we can all confidently say would work just fine.

On the right-hand side is an example of one that was low. So at 250 copies per mL when you start it, you're actually starting with 50 copies total in your elution. After the elution, you have 50 per 100 µL, and so you're putting 5 copies into the PCR well.

So when you think about that just a little bit, that means you've got 50 copies wandering around in 100 µL. If you put your pipette in and pull out 10, what are the odds that you're going to get 5? It's probably actually not very good. Sometimes you're going to get 4, sometimes you're going to get 3, sometimes you're going to get 8. And so that's where the variability comes from. And so when -- down at those lower levels, it's much more difficult to consistently get the same result.

So here's the example of how we deal with that. We have decided that we're going to talk about our assay sensitivity as where does it go from being positive all the time to being positive only sometimes? So we're using, sort of as an industry standard, 95%. So this is an example of titration of a sample that's high, over on the right-hand side, and as you dilute it, you get less and less of a percentage of the samples that are going to be positive.

So this is the example of the kind of data that we do with this. We take -- make a little serial twofold dilutions, and we run multiple replicates. This is an example of six, which is the minimum number that's recommended, but it's not a very statistically good

number. Probably 40 or 50 or 100 is much better but very expensive.

And so the examples where the circles are, as you dilute these two different patients, you can see that one of them goes from being positive to negative in that middle column, at 109 copies, is the last one that's positive. The next one is not positive in all the replicates. And in the second to the last column on the right, the last one that's positive is 148. So if this were a single assay, you would say, well, our cutoff is someplace between 109 and 148. So although we can talk about our assay sensitivity being 150, in this particular example, it's only an average, and the reproducibility of that number is not particularly good.

All right, so let's talk about sensitivity as it relates to clinical results. So on the right-hand side, I've got a nice little sort of swelling, motions up and down, waves. And that's pretty much what we're looking at for a number of our patients. When we have a good, sensitive assay, we can see a lot of patients who have a little bit of reactivation but not real disease. And we're trying to distinguish that from the beginning of a big wave of CMV that might be associated with disease. So our reproducibility and our sensitivity are both a function of how well it works for you clinically in the lab.

So our assays are very imprecise during the range before we get to 95% all the way down to 1%, so not very reproducible. So, hence, we start talking about the limit of quantification versus the limit of detection. So limit of detection is usually called the 95% limit. The limit of quantification is usually up from there a little ways. But what do we do about all the ones in the middle that are positive sometimes and negative sometimes? There's a lot of debate about that, and I don't think there's a clear idea about how to do it at this point, very confusing strategies.

One of the questions is we now have something called digital PCR. I'm not going to spend time talking about it, but digital PCR is a more precise, accurate way to do it. This is

from a recent study that we published, trying to say if we had really accurate digital results, could we more quickly tell whether someone was going to be positive and have an actual episode or not?

So on the right-hand side are the individual results, comparing digital to real-time PCR for 19 patient samples. And I've highlighted the one on the left-hand side, which is one that actually was monitored over time and actually had an episode. So you can see pretty much it didn't really matter. The increased reproducibility of the digital didn't really help that much to predict the actual episode. And so you can review that paper if you have any more questions or ask me about that later.

All right, so what about standards and primers and probes? So currently, for CMV, there is an international standard and a NIST standard. The international standard is built to be able to make a 1 to 2 dilution into a matrix, whole blood or plasma. The NIST standard is purified DNA and is used just in the PCR step. Then there are a number of secondary reference materials made by several commercial sources that we can use. None of these are available in the kind of quantities that can be used on a regular basis.

As far as standards go, there are two basic approaches. One is that the instrument that you're using has the ability to store a standard curve. And so you do it once, and you must do it at least once every 6 months, according to current guidelines. If you don't have an instrument that does that, then you have to run a standard curve with every run. So must of us use plasmid clone preparations that have been compared to the international standards, and we either clone the amplicon itself or an area around the amplicon that we're using.

So the purpose of the standards is to assign the correct value to our standard. And we're trying to assure the value doesn't change over time within a single lab. And we're trying to assure that the same value is obtained across multiple methods and across

multiple labs.

So here's a quick example of some really bad data before the standards existed, published in 2009, and you can see that the spread of the results for CMV for this was about 4 logs across and was true regardless of the level of the sample. So something that was 200 and something that was 10,000, both of them were quite variable.

So are we doing any better now? So this is post-WHO, and first what I need to talk to you about a little bit would be what is commutability?

So here is the -- there are the two statements out of regulatory documents. I won't bother to read the whole entire thing, but basically, the idea is, is your reference material able to be the same as a patient in your test, so does it perform exactly as a patient specimen, or is it somehow different? And number two, does it work across multiple methods? And so those are the things that we want to know about our standards.

So here is just a little bit of data from a fairly large commutability evaluation published last year. This is an example of two assays that don't work very well together, so commutability, on one level is, how does one assay compare to another one, and how does the standard work?

So here are two assays that don't work very well. You can see that, in both cases, the international standards, which are the bars, the red bars, are not looking the same as the patients' and don't have the same slopes. So neither of these two assays, the WHO material is not commutable.

This is a summary of that data, with all the different laboratories and all the different results. The green ones are commutable within each other, so the top one is not commutable, and a number of them are not commutable. So we have a long ways to go when we're looking at a whole bunch of different assays to get them to agree with each other.

This is more of that same data, published in a different paper, which gives you an idea. The upper left is the results for the international standards with all the different assays. So even though we've all standardized with the standard, when we ran the standard, we didn't get a very good agreement. And the right-hand side are patient data samples for those same assays after everyone standardized, so still a lot of variation across those labs.

This one is an article that talked about, okay, does the WHO strategy of taking material that they've cultured, and then they give it to us, and we should dilute it 1 to 2, into either plasma or serum, does it work? And it turns out that this publication advocates the fact that actually, this standard doesn't work in whole blood because all the standards, which are the ones in the blue, are off and do not react in the same way the patient samples do.

So primer and probe design, just a couple words about that: There's a very large study, published in 2009, that identified 82 primer and probe sets in the literature, checked them all. Most of them didn't match with alignments. Ultimately evaluated 17. Finally found three that were primer sets, all in the gB region that were the most sensitive, and found that the best ones were usually the smallest ones. So the smaller the primer and probe set, the more efficient, and therefore, the more sensitive.

And this is a paper that was published recently that described a patient who -- actually, they were comparing their in-house to a commercial assay. And their in-house assay, they were following serially a bunch of patients, and one patient suddenly just didn't agree. And it turned out they had developed a mutation underneath a primer set. And so this is an example of if they made an alternate primer for that particular sequence, they could do it correctly.

I show this slide because there's a lot of advocates who would say that you have to

have a couple of primer sets to make sure that this is the kind of thing that doesn't happen. So many of us have two primer sets in our primer and probe sets for our tests.

So here are the currently FDA-approved CMV quant tests. There are two of them. And they are really only approved for transplant monitoring in both cases.

So with that, I'll stop, and I guess we'll field questions.

DR. PETTI: Thank you, Dr. Cook.

I'll ask the Panel if there are any brief clarifying questions for either Dr. Cook or Dr. Limaye.

Yes, Dr. Kotton. Please state your name --

DR. KOTTON: Camille Kotton.

DR. PETTI: -- for the transcriptionist.

DR. KOTTON: Camille Kotton, Boston. Could you go back to your last slide? And could you just clarify whether -- you or your delegate could clarify whether these are approved for just blood assays, or are they approved on tissue on the NBAL and other specimens?

DR. COOK: Nothing is approved on tissue.

DR. PETTI: And is that --

DR. COOK: And I think that the original solid organ monitoring -- someone else might correct me, but I think the original Roche assay was whole blood. I'm not sure that's true with the new version as well. And I think the other one's plasma, but someone who knows better should probably correct me.

(Off microphone comment.)

DR. COOK: They're all plasma? Thank you.

DR. KOTTON: What did she say? Sorry. I didn't --

DR. COOK: She said they were all plasma.

DR. KOTTON: Thank you.

DR. COOK: I know the original, non-FDA one from Roche was a whole blood assay.

DR. KOTTON: And is the whole discussion today just about whether these could be used on blood specimens? Or is there any discussion about other specimens today? Just for clarification.

DR. PETTI: Dr. Gitterman.

DR. GITTERMAN: For today's discussion, we're talking -- of course, you can make out-of-scope questions, but really the reclassification is for the assays for CMV in blood.

DR. BADEN: Actually, plasma. I mean --

DR. GITTERMAN: Correct. Correct.

DR. BADEN: -- because I think the precision here is not trivial.

DR. GITTERMAN: Correct. Absolutely.

DR. PETTI: Dr. Baden, please --

DR. GITTERMAN: Absolutely.

DR. PETTI: -- state your name before you speak.

DR. BADEN: I'm sorry. Dr. Baden. And I just spoke. For Dr. Cook, will we have a chance to ask more questions afterwards as part of the opening discussion, or now is our opportunity to get more information from her?

DR. PETTI: We can ask the speakers to come to the podium at a later date. Yes.

DR. COOK: Okay. Thank you.

DR. PETTI: Thank you.

I now ask Dr. Kathleen Whitaker of the Division of Microbiology Devices at the FDA, who will provide FDA's perspective on benefit/risk of reclassification.

DR. WHITAKER: Okay. Thank you and welcome.

I am at present a scientific reviewer in the Division of Microbiology Devices, and I'll

give you the perspective on reclassification for CMV viral load assays. And I guess we'll take questions at the later time.

Okay. Some of this you may have already heard, so I'm just going to go through this somewhat quickly, and we'll -- a couple of slides later, we'll have more detail.

What we have here on this slide is a general schematic of how knowledge and risk of an analyte and device interact, for FDA to ascertain the proper placement of a device into one of three classification groups. Devices or analytes for which there is the highest risk to a patient and for which we have the least knowledge are placed in Class III. It's possible, as our knowledge of a device or analyte increases, this may mitigate the risk of the device, allowing it to be placed in one of the other groups.

So here we have an explanation of what constitutes controls for each group. As a device class increases from Class I to Class II to Class III, the regulatory controls also increase, with Class I devices being subject to the least regulatory control, and Class III devices being subject to the most stringent regulatory control.

For Class I devices, here in vitro diagnostics, manufacturers are required simply to list their establishment and the devices they market. Manufacturing, in all cases, must be done using GMPs. Labeling is done in accordance with the appropriate C.F.R. regs, and adverse events are reported. For Class II devices, controls are specifically tailored to each device, which is what we'll discuss today, and for Class III, a PMA is necessary for approval of the device.

So what are Class I devices? These are devices for which general controls are sufficient to provide reasonable assurance of safety and effectiveness. Class I typically do not require FDA premarket review, although there are limitations which can be tripped where they do need FDA review.

And what are Class II devices? They cannot be classified into Class I because general

controls are insufficient to provide reasonable assurance of the safety and effectiveness of such device, and for which there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification, a 510(k), and review prior to being marketed.

So when is a device Class III? It's purported or represented to be used in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or it presents a potential unreasonable risk of illness or injury, in essence, a device that cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness.

Here we have a slide which kind of lists what is necessary for approval of a PMA. There must be valid scientific evidence that the probable benefits to health from the use of the device, when accompanied by adequate directions and warning, outweigh any probable risk. Similarly, based on valid scientific evidence, there is reasonable assurance the device is effective under the same conditions as we just stated.

And let's look at what FDA requires normally in a PMA and 510(k) applications. These are the data requirements for both premarket applications and premarket notifications. I won't read through all of these, but you can kind of get an idea. I'm sure everybody has seen these before, precision, accuracy, limit of detection has come up, etc. When going from Class III to Class II, there is no loss of analytical information with reclassification.

So what's different about Class II and Class III devices? PMAs, Class III, contain a manufacturing section in their submission, which is not required when submitting a 510(k). Now, that's not to say that similar studies are not performed for a 510(k); however, they're simply not required to be submitted. Manufacturing information must be retained at the

site.

Pre-approval inspections are done at the site of manufacture for all Class III devices as BIMO, or bioresearch monitoring visits. The BIMO inspections ascertain that samples were collected appropriately, and data integrity of a submission has been maintained. 510(k)s do not require annual reports, and the studies carried out for PMAs, just by the way, often contain multiple lots and materials which 510(k)s don't.

So when is downclassification appropriate? Class III devices, as previously mentioned, can be downclassified to Class II when sufficient information becomes available to establish special controls that will reasonably assure safety and effectiveness.

We already heard a little bit about this in the first talk, but in order to downclassify, we first have to address what are the risks to patient health should there be an inaccurate result? For example, a falsely low or even negative result may lead to inappropriate patient management, such as premature discontinuation of antiviral therapy. On the opposite side, a falsely high or a false positive result may lead to unnecessary treatment or unnecessarily prolonged treatment of a patient.

We might also want to consider, with increasing decentralization of follow-up and restrictions on test selection, increased risks of patients being exposed to measurements of CMV viral load by tests from different sources. Variability across different devices may lead to increased patient risk as viral load is measured by different devices, even if each device is performing accurately.

At this point I'd like to look at what types of special controls are available for the Panel to consider for CMV viral load assays. We have the ability to specify what the labeling should contain. For example, we could also ask for specific manufacturing information, method comparison studies, analytical studies, clinical performance studies, and even postmarketing studies, if we wanted to put that in the special control. And each of these,

we'll go through here. And also, please note that these do not represent all possible special controls.

All right, for device labeling, if it's deemed necessary, we can place a warning in the labeling, stating a patient must or should be followed using the same assay prior to and post-transplant. We can incorporate medical guidelines or recommendations to follow these guidelines in the labeling. We can include the need for manufacturing information, as I just mentioned, such as how traceability to a standard is maintained and how manufacturing specifications will be instituted to ensure that the final product meets all design specifications.

Okay. The analytical studies, as I mentioned, we kind of went over those, but a couple of the things that we can do in the special controls for analytical studies, one such control may be comparison to a recognized standard and an FDA-accepted comparator method. We could include predefined maximum allowable total difference zones between the new assay and comparator test, as well as maximum deviation from linearity, similar to tolerance in current PMAs.

Maximum allowable total difference zones between the new assay and comparator test can be specify -- I'm sorry. These are -- and right now, we currently have two standards that can be considered for use in these studies, as you've just heard, so I won't go into those a lot, but the NIST standard, and the first international WHO standard.

In terms of clinical performance, special controls can be written to specify populations that should be tested in the clinical study, whether the use of prospective of retrospective specimens is permissible, or maybe both, how the distribution of samples are in the 510(k), what comparison methods can be used, and whether the use of contrived specimens is appropriate or not, as well as whether to include a longitudinal study of patients in response to treatment.

Okay, we were thinking about possible postmarket controls, and some of these may include studies to demonstrate an absence of drift in assay performance and confirm that inclusivity is maintained. For example, these could be internal sponsor studies to verify performance to an acceptable FDA standard and just the results simply maintained on file.

Within the 510(k) submission, the manufacturers could describe an accepted method of risk assessment, to provide a framework for systematically managing risk when modifying the device. This would be in addition to proposed FDA draft guidance on this issue. And based on these studies, the sponsor may or may not need to submit a new 510(k). Some examples of changes that wouldn't likely need FDA review would be modifications of additional probes, new primers, and other enzymes.

And then finally, I get the Panel questions that Steve Gitterman, Dr. Gitterman will provide later in more detail is do the Committee members believe that special controls, in addition to general controls, are necessary and sufficient to mitigate the risk to health presented by quantitative CMV viral load assays?

And as a follow-up to this question, in the discussion of special controls, please address the following. And again, we've just heard about this from the previous speaker, so in the interest of time, I'll cut that.

And then finally, thanks to the many members of our Division of Microbiology for help and assistance in putting this together.

DR. PETTI: Thank you, Dr. Whitaker.

Does anyone on the Panel have a brief clarifying question for Dr. Whitaker?

Yes, Mr. Simon.

MR. SIMON: Tom Simon.

Can you define what the risk is, what is safety, and what is effectiveness, because they all contradict each other. What is the risk, and what is the cutoff point for the risk?

Safety and effectiveness, also.

DR. WHITAKER: Right. I think that's what the Panel are kind of here to discuss and determine whether -- I mean, is the risk of an inaccurate result to a patient enough that we can downclassify and ask for less controls and less overall management of these tests when they come in to the FDA to look at them? Or, you know, is the risk of an inaccurate result too high, that we're going to have patient morbidity, mortality, or something? So is that what you're --

MR. SIMON: So the consequences of the three?

DR. WHITAKER: Right.

MR. SIMON: Okay. I'm just having a problem with where is the cutoff point? Say, in your determination of CMV viral tests now, which are Class III --

DR. WHITAKER: Right.

MR. SIMON: -- what's the cutoff point between Class III and Class II?

DR. GITTERMAN: Perhaps I would suggest that maybe during the next phase we could ask Dr. Limaye to come back and perhaps address that. Would that be fair?

DR. WHITAKER: It is. It's not where I can actually draw you a line. I think it would be good to have discussion on that.

MR. SIMON: Having been a patient in several things, that's why I'm confused. Thank you.

DR. PETTI: Yes, Mr. Flatau.

DR. FLATAU: Hi. Arthur Flatau.

I just had a quick question. You talked about comparator methods, and there's an FDA-accepted comparator method. So are the NIST and the WHO comparators of those FDA accepted or not?

DR. WHITAKER: Well, they're the ones we currently have at our disposal, and I think

we're accepting of those standards right now. Again, it's -- okay.

DR. GITTERMAN: Well, that's a very good question. Going forward, under a PMA, we could individualize based on the specific assay, based on the evolution of knowledge, based on what people have done before, based on even comparison to previous assays. We have a lot of capabilities at this point, under PMA, that give us a lot of flexibility. If were to go into a 510(k) paradigm, we'd have to really be more specific. You could write a 510(k) control to say that you can use any of them or one of them. That's one of the things we're looking at for discussion.

And as Dr. Whitaker pointed out, that's sort of part and parcel of the second question. So is the science at a point where we can be specific and make recommendations? Or does it really need to be more of a PMA paradigm, where we can give specific guidance that evolves and have sponsors address it on an individual basis?

DR. FLATAU: So you would -- that's part of the -- or it's part of the, whatever, your ruling, you would define what the comparator, whatever, after -- I mean, if we accepted this, you would have to define them?

DR. GITTERMAN: We would. And we -- again, I don't want to limit the Committee's discussion. We could say something like you could use any comparator, or we could use, to use one comparator, because there's advantages and disadvantages of each, which we could talk about during the --

DR. FLATAU: No comparison.

DR. GITTERMAN: That really is on the table.

DR. FLATAU: Okay.

DR. WHITAKER: And we could be as specific as we, as specific as the Panel believes that we should be, or we could be a little bit more general, just saying an FDA comparator method, putting that in the regulation, or we could be very specific and say you have to use

the NIST standard and do, etc., etc., etc. So it's kind of a wide open concept here on what the Panel believes is -- or, in combination, of acceptable.

DR. GREEN: Michael Green, Pittsburgh.

I just want to clarify. So in contrast to using a standard, I think we also could potentially use, I think you said, like putting the new, prospective new product against an existing FDA-approved product like the cobas test.

DR. WHITAKER: That's one, another possibility --

DR. GREEN: Thank you.

MR. BRACCO: This is Dan Bracco from Roche.

In regulatory lingo, that would be called the predicate device, Dr. Green.

DR. PETTI: Dr. Meyer.

DR. MEYER: Dan Meyer, from Dallas.

Quick question: How would a specialty control, such as looking at the clinical performance studies, you know, that you could follow, how would that differ from the premarket data requirements of, you know, precision and accuracy that are required for a Class III device? Because you'd be looking at, you know, pretty similar endpoints in both of these requirements. How does that differ?

DR. WHITAKER: Well, for the analytical studies, for precision and what was the other one?

DR. MEYER: And accuracy.

DR. WHITAKER: And accuracy, they'd be essentially the same for a PMA and for a 510(k).

DR. MEYER: Okay.

DR. WHITAKER: Though not -- rarely do the analytical studies change between the PMA and 510(k). The only thing that may, you know -- that normally would change is if you

have a quantitative or a qualitative assay and looking at, as we mentioned before, lower limit of quantitation or upper limit of quantitation.

DR. MEYER: They'd be of the same scrutiny --

DR. WHITAKER: Yes.

DR. MEYER: -- in the special controls?

DR. WHITAKER: Yes. Yes, absolutely.

DR. PEREIRA: Marcus Pereira from Columbia University.

So for the existing standards that we have so far, should those be updated in the future? Would there be the ability to change the test based on those new standards? Or how would that work?

DR. WHITAKER: I believe so. Again, I would have to see. I would have to be kind of careful in crafting a regulation. And that's kind of, I'd say, I believe, the rationale for putting in an FDA-accepted standard, so that we could evolve as the times evolve, rather than saying, you have to use the WHO -- the first international WHO standard. If we said an FDA acceptable standard, that would allow for evolution as the --

DR. GITTERMAN: Right. But if the question is could we take a product that's been, let's say, cleared against an earlier version of the standard that's been marketed, approved, or cleared, and then, in fact, say you need to go back and do that, the answer is, unless there is evidence that the product had changed or a risk to health, they're just likely not.

So if you market a device now that may be shown to be outdated, in fact, it's very difficult to recall that from the market. And we have examples of that. I'm not going to go into -- actually, I might mention one later this afternoon. But that is one of the benefits, in fact, of having the PMA paradigm. There is more variability.

DR. PEREIRA: So were the standards used for the Roche, and for the currently FDA-approved tests, were they used -- the WHO or the NIST or none of these standards were

used for this test?

DR. GITTERMAN: They -- now, again, perhaps you --

DR. WHITAKER: I think -- I believe that the majority -- I believe they did do something, and Lee can answer, using the WHO standard, but the majority of the performance in that was calculated from specimens from the VICTOR study, correct?

DR. GITTERMAN: Right. I believe the W -- now again --

DR. WHITAKER: There was some linearity, I think.

DR. GITTERMAN: Right. They did do the WHO standard as part of their studies, but it was late in the game.

DR. WHITAKER: Yeah, it was.

DR. GITTERMAN: And it was -- and then -- yeah. When they started developing the test, it was not in existence.

DR. BADEN: So -- Dr. Gitterman.

Just a follow-on: If something is cleared or if something is approved, so Class III, then a new device, through the predicate concept, can then be cleared, even though the original may not meet the new standards?

DR. GITTERMAN: In a Class II, that potentially could be the case, yes, and in fact sometimes is the case.

DR. BADEN: Yes. Yes. Now that's --

DR. GITTERMAN: Because I will -- well.

(Off microphone comments.)

DR. GITTERMAN: I think Dr. Petti's intention was these be brief clarifying questions. We all will be back. Nobody's leaving.

DR. PETTI: Yes. We have a nice Panel deliberation session upcoming. Any other clarifying questions for Dr. Whitaker?

(No response.)

DR. PETTI: Thank you. Let's take a 15-minute break, and convene at, let's say, 10:05. It will be a little less than 15 minutes.

Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any other member of the audience. Thank you.

(Off the record at 9:53 a.m.)

(On the record at 10:08 a.m.)

DR. PETTI: Please take your seats. We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Ms. Asefa will now read the Open Public Hearing disclosure process statement.

MS. ASEFA: 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 relationship 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 travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PETTI: There have been two formal requests to speak. Dr. Edward Evantash will speak on behalf of Hologic.

Dr. Evantash, you have 10 minutes.

DR. EVANTASH: Do I have slides?

DR. PETTI: Yes.

DR. EVANTASH: Terrific. Thank you.

And thank you to the members of the Panel and the FDA for this opportunity to speak on behalf of Hologic in support of the reclassification of the in vitro diagnostic assay, CMV viral load, from a Class III PMA to a Class II device.

I am Dr. Edward Evantash. I am the Medical Director at Hologic and the Vice President of Medical Affairs at the company. I think that speaks for my financial affiliation with the company. And I wanted to speak to the rationale for the downclassification, as outlined by our colleagues earlier.

First, the clinical utility of CMV viral load assays has already been well established. We have predicate devices that have already gone through the PMA process and established the clinical usefulness of this device with respect to safety and effectiveness, monitoring patients' antiviral therapy and immunosuppressant medication based on the viral load assays that were obtained.

For that reason, when we look at the need for going from a Class III to Class II, not having to do those longitudinal studies is an added benefit for allowing more devices to be used for patient care.

Therefore, demonstrating equivalence to the currently approved predicate devices is sufficient to determine the safety and effectiveness of the CMV viral load assays. We currently have a predicate device that has gone through a PMA process, and calibrating and validating to show substantial equivalence, both to that predicate model as well as to the World Health Organization international standard, provide adequate chronification to CMV DNA across the assay range and showing consistency.

Furthermore, the devices in a 510(k) needs to be sensitive, demonstrate sensitivity and provide precise, reproducible, and reliable quantitation across all the CMV genotypes.

We recognize that there are risks, and identifying those risks as well as the mitigations is an important process and is also part of the 510(k) paradigm. Over-quantification may lead to improper treatment and possible patient harm, either by decreasing immunosuppressant medication or by increasing antiviral treatment. And under-quantification may lead to inappropriate treatment or initiation of preemptive therapy.

But for that, the risk mitigation exists, and I think this gets to Mr. Simon and Mr. Flatau's point about what controls exist to provide assurance of safety and effectiveness, and that's achieved through labeling and interpretation of the results that are provided to the user, as well as, and most importantly, the analytical and the clinical studies that are part of the submission to the FDA.

I want to talk about the special controls. First is the labeling and the intended use. This is an in vitro nucleic acid amplification test for the quantitation of human cytomegalovirus DNA in human plasma, serum, or whole blood. And the assay is intended for use as an aid in the management of solid organ transplant patients who are undergoing anti-CMV therapy.

The test measures CMV DNA levels in human plasma, serum, or whole blood and can be used to assess virological response to antiviral drug therapy. The results from the assay must be interpreted within the context of all relevant clinical and laboratory findings, and the assay is not intended for use as a screening test for the presence of CMV DNA in blood or blood products.

An example of how results would be interpreted across the range of all values, and how we use this clinically, including values above and below the limit of quantitation.

Analytical studies are intended to mitigate the risk, to reduce variability across these assays. And this is done with a comparator, either, as we mentioned before, the recognized predicate assays that have already been FDA approved, but ultimately demonstration of new product as through the 510(k) process of precision, accuracy, sensitivity, and specificity.

Additionally, because many of these patients have other opportunistic infections or pathogens, are also on multiple medications, analytical studies include evaluation for cross-reactivity as well as interfering substances.

Further special controls would include clinical studies to demonstrate substantial equivalence, using patient samples, relative to the previously approved predicate devices. Method of comparison correlation studies would be required that would compare this assay to those previous devices, and this would be a statistically justified sample size included in these studies based on the assay precision and linear range.

In addition, to reduce assay variability, clinically reproducibility studies would be required as part of an FDA 510(k) submission.

Based on the establishment of clinical utility by the currently approved CMV viral load assays and the associated product risks, Hologic concludes that special controls, specific to the assays, are sufficient to provide reasonable assurance of the safety and effectiveness of nucleic acid-based in vitro diagnostic devices for the quantitation of human CMV DNA.

Therefore, we recommend downclassification of the IVD devices for the quantitation of CMV DNA in human plasma, serum, or whole blood, from Class III to a Class II, with special controls as outlined by the FDA in agreement with the company during submission.

I'd like to thank you for your time and answer any questions that the Panel may have.

DR. PETTI: Thank you, Dr. Evantash.

Yes, Dr. Baden.

DR. BADEN: Can you go back to the last slide? Just want to make sure I understand, you're looking for a Class II 510(k) predicate comparison?

DR. EVANTASH: That's correct.

DR. BADEN: And it's plasma, serum, or whole blood, yet the current predicate is only approved for plasma. So how does it -- how do we extend to the other matrices?

DR. EVANTASH: So I think that would be part of a FDA submission and conversation, to demonstrate equivalence between the various samples and to confirm that there is limited variability and that those biases are acceptable to the FDA.

MR. BRACCO: This is Dan Bracco.

If I could just clarify that there are no predicate devices right now, because it's a Class III device. What happens is if the device goes to Class II, then any existing product out there would then be eligible to be a predicate device.

DR. PETTI: Thank you, Dr. Evantash.

DR. EVANTASH: Thank you, Dr. Petti.

DR. PETTI: Mr. Jonathan Nurse will speak on behalf of the Infectious Diseases Society of America.

Mr. Nurse, you will have 5 minutes.

MR. NURSE: Good morning. My name is Jonathan Nurse, and I'm Director of Government Relations for the Infectious Diseases Society of America. I have no financial relationships or conflicts to disclose. I have simply a brief statement from IDSA.

IDSA is pleased to share our comments regarding reclassification of quantitative CMV viral load devices, and initial classification for qualitative or quantitative viral load devices for Epstein-Barr virus, BK virus, JC virus, human herpesvirus 6, and adenovirus

infections. We urge the FDA to classify viral load tests for these transplant-associated viruses as Class II.

Patients who receive solid organ, bone marrow, stem cell transplants are at greatly heightened risk of opportunistic viral infections, which can significantly complicate their clinical course. Viral load tests provide invaluable information to allow for accurate diagnosis and monitoring of infections for transplant recipients. Categorizing these viral load tests as high risk is inappropriate and can limit availability and innovation.

The management of these infections has become routine for transplant specialists. These viral load tests have been in use for many years, with well-documented data demonstrating clinical ability and peer-reviewed literature supporting their use. The standardization of assays in clinical care for patients with transplant-related viruses has allowed for the establishment of strong expert guidelines. Managing patients post-transplant with viral load tests is the standard of care.

The risk associated with the use of transplant viral load tests is further mitigated by additional factors. First, patients are typically tested multiple times, with clinicians regularly viewing results for consistency. Second, clinicians utilize additional factors beyond an individual test result, including pathology, radiology, patient history, and clinical context to guide and inform clinical decisions.

In May, IDSA provided FDA a selection of literature supporting the use of viral load testing for transplant-associated viruses. IDSA also encourages the Panel and FDA to consider the risk posed by classifying these tests as Class III or high risk, namely significantly diminishing patient access to testing. There are currently only two FDA-approved tests for CMV on the market, and there are no FDA-approved tests for many other transplant-related viruses.

One reason for the paucity of FDA-approved devices for transplant monitoring is the

requirement for companies to seek approval through the PMA process for Class III tests. A PMA would require multimillion dollar, multi-site clinical trials. Additionally, the volume of transplant testing is limited, making the return on investment difficult to attain.

A reclassification to Class II should lead to significant reduction in clinical trial costs, faster time to market, and therefore encourage commercial companies to seek FDA clearance. More FDA-cleared devices would give laboratories options when selecting a device best suited for their testing and clinical needs.

In addition, by classifying viral load tests for transplant-associated viruses as Class II or moderate risk, the FDA can delay and lessen the disruption to care for transplant patients that the proposed laboratory-developed test regulatory guidance would be, would likely otherwise cause.

Many of the current tests in the space are LDTs. Under FDA's proposed LDT regulation, high-risk LDTs would be the first to face a new oversight. The vast majority of clinical laboratories would very likely be unable to bear the enormous cost of PMA submission, resulting in very few testing options to guide the care of transplant patients.

BK polyomavirus is one example of a transplant-associated virus for which access to rapid viral load testing is critical. Currently, there are no FDA cleared or approved assays for BK virus on the market. BK is the major cause of polyomavirus-associated nephropathy, putting 1 to 15% of kidney transplant patients at risk of premature allograft failure.

Given the lack of effective antiviral therapies, screening kidney transplant patients for BK is the key recommendation to guide the reduction of immunosuppression in patients with BK viremia. This approach allows for a clearance of BK infection in 70 to 90% of patients. Late diagnosis is accompanied by irreversible functional decline, poor treatment response, and graft loss.

Guidelines published in 2013 in the *American Journal of Transplantation*

recommended regular BK screening. If physicians lose access to tests for BK, there are significant risks that many with BK infections will not be identified properly and will thus lead to negative patient outcomes.

IDSA greatly appreciates the opportunity to provide comments on this important issue, and we look forward to a continued dialogue with the FDA to guide policy making in this area.

DR. PETTI: Thank you, Mr. Nurse.

Questions?

Yes, Dr. Green.

DR. GREEN: Mike Green, Pittsburgh.

I'm not sure if this question is for Dr. Nurse, but perhaps for Dr. Gitterman, and that's clarification for us to think about the proposed laboratory-developed regulatory guidance that was referred to in the IDSA comment, because I'm not aware of that, and it seems like it has implications on what we're doing here today.

DR. GITTERMAN: I'm glad you asked that question because I did want to make that clarification. Draft means draft. This is being put out for public comment. I don't think anyone in this room can say if, in fact, those drafts will, in fact, emerge as any type of regulations you're going to -- whether they'll even ever emerge, period -- or, I'm sorry, final guidance.

And I would urge the Committee, in many respects, not to look at that. You know, many things are -- you know, not all draft guidance ever becomes final guidance, in which case, it has no, you know, regulatory effect. And from draft to final, especially something as significant as the draft guidance for laboratory-developed tests, which would probably touch all of us, in fact, you know, FDA will respond to all the public input.

Again, I cannot comment -- it's not my place to comment on the specific points that

Mr. Nurse had said, but I would strongly urge that that not be a consideration for the Committee, because basically no one knows. And if it -- you know, it would be hard for us -- and I have to also say, it would be hard for us, in our considerations, to use that information if there was such a -- and for someone to say I am doing this because I am concerned, that would not be a factor we could take into it because it's not a regulatory issue at the present time, and it's absolutely uncertain, not only that as an interpretation, I mean that being true for any draft guidance.

So it's a very good question, and that should be off the table essentially.

DR. PETTI: Does anyone in attendance wish to address the Panel?

(No response.)

DR. PETTI: Does the Panel have any additional questions for Open Public Hearing speakers?

(No response.)

DR. PETTI: I now pronounce the Open Public Hearing to be officially closed. We will proceed with today's agenda.

We open the floor to the experts around the table to begin deliberating on any issues that you may have with any data you've heard today, either in the Panel presentations, the discussions with the FDA, or the material that you have read in your Panel packs.

Although this portion is open to public observers, public attendees 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. This helps the transcriptionist identify the speakers.

Do any Panel members have a question or comment for the FDA?

Yes, Dr. Flatau.

DR. FLATAU: Arthur Flatau.

So I guess, you know, I don't understand a lot of what was talked about this morning. I understand a few things. But I think it's fair to say that the CMV testing now is far from perfect. But what I don't really see is how it being classified as a Class III device, these devices, Class III devices, how that increases patient safety or increases the efficacy of the test or any of those things.

DR. GITTERMAN: That's a fair question. For one extent -- and a lot of it is what regulatory oversight does FDA have? When the submission comes in, as Dr. Whitaker put it, all the manufacturing information is submitted. So we have very, very good insight. Now again, through special controls, we can request some of that. But we'll have very, very good insight into the quality of the test, how well it -- you know, what those aspects of the test, the following with the quality system, etc.

We have the ability to do an inspection at that time. We often do -- obviously, if a manufacturer has recently been inspected, we may not inspect him at the time of submission. That would be fairly redundant. But if that is not the case, then in fact, they will be inspected. So we can have greater assurance that, in fact, the submission is accurate and they are, they have -- following quality systems and the data's accurate.

As was said before, we have the biomedical inspection where we can do -- you know, ensure that, in fact, the samples were tested, that samples weren't thrown away, that accurate information was established, that samples were not retested, as may occur, that basically, again, the confidence that, in fact, the manufacturer followed the instructions.

As people talked about, as things evolve, again, it is easier to ask for revised requirements to individualize what is necessary from a specific assay, depending what the technology they use. But again, some of that is -- I won't deny that some of that is available also in a 510(k).

The issue -- and still come up -- it's sort of more of a point that if you change a device substantially from a 510(k), it has to -- it gets a new 510(k). But all the supplements to a device as a PMA, virtually every change in a PMA -- and I said virtually, not all, will come as a supplement and be reviewed to ensure the quality of the device and to ensure it won't have a significant effect on the outcome.

In the 510(k) paradigm, it's a little less stringent, and manufacturers have the option for themselves to determine what a significant change would be, and how they, in fact, justify it. Or changes that are less than those have to be -- that they determine not to be significant enough to be reported to the FDA, they have the option of doing what they determine their own validation, and you know, sometimes that may or may not raise questions.

Depending on the labeling, we may have more control over the labeling of exactly what is said, what is not said. And again, the postmarketing requirements -- like let's say people wanted less data at the time of marketing. We have programs for the PMA, sort of like all the expanded -- the expedited access program, where we can approve a device on less data and then, in fact, follow it up with additional postmarketing data which the company is then required to submit.

There's a number of other aspects, but I would suggest the bottom line is we have much more confidence, much more to review in the original data. I think the public can take much more confidence in the results, especially for an area which now -- and your question's a very good one because things have evolved, as we know. This is a very different circumstance than it would have been 10 years ago. But it gives -- you know, it gives us and the public much more confidence in the accuracy of the information, of the means that the sponsor may have to confirm that accuracy, the materials that we've reviewed and the depth of materials that's provided for that accuracy.

And again, in the post-approval phase for the PMA application, we have much more oversight and control. There's annual reports that come in, just as another thing, for the PMA process, which doesn't, you know, doesn't occur.

There's not that many reclassifications, and the fact is, we don't -- you know, for the reasons you were asked, there are -- you know, in our division, there actually aren't, you know, relatively large number of PMAs for exactly that reason. But something like CMV, which could have life and death -- I'm extreme, but this can have tremendous morbidity to these patients and especially for reasons that came up before, since there really isn't some established threshold, since it's -- you know, there is decentralization of, I would say decentralization of care, but what I really meant to say is decentralization of testing.

There's the more control, especially if there's a slightly different technology for us to really be certain that it's measured accurately. And again, as the Committee will talk about, what the changes for accuracy are, you know, what the -- as we'd say in the old, they have just noticeable differences, or what the parameters between tests are, because it is a fact, the more tests that get out there, especially if they're less carefully reviewed, the less commutability there's going to be, and the greater possibilities there are for errors.

And it's, you know, the -- I hope that's -- is that sufficient, or do I need to provide more details?

(Off microphone reply.)

DR. BADEN: I have a question for Dr. Gitterman and a question for Dr. Cook.

Dr. Gitterman, the LDTs, what is the current oversight standardization for LDTs, which are obviously laboratory-developed tests and therefore individualized?

DR. GITTERMAN: In terms of regulatory oversight?

DR. BADEN: Correct. As one thinks of comparability across LDTs for testing in the space, how one manages that variability.

DR. GITTERMAN: Could I say none?

DR. BADEN: That's what I thought. Thank you.

DR. GITTERMAN: Could I say that's markedly by the --

DR. BADEN: Succinct answers are appreciated.

Dr. Cook, for the WHO standard, the NIST standard, what are the barriers to scale-up, for that to be able to be more universally utilized, and therefore, would that -- what are the barriers to scale-up, and if there were scale-up, would that allow comparability between different testing centers?

DR. COOK: Well, so the WHO process creates a whole bunch of vials. They life-lyse and then throw into some place that will store it, hopefully indefinitely. But what they actually end up doing is making International Standard Number 1, and then International Standard Number 2, and International Standard Number 3, and each one of them are slightly different from each other. And so things like HIV, HCV -- I think HCV, the international standard is on version number 7 or something like that, in the last 20 years. So that's the issue with that.

The other issue is that those are actually, primarily come from commercial -- or from clinical samples. And so they're probably a little more like an actual patient sample than are the CMV and the other standards that we're going to talk about later on. So that's the issue with that.

The NIST stuff actually came out about 6 months after the original WHO material came out and unfortunately within a year had some stability issues because it was pure DNA, and we sort of understood a little bit less at that point about how to do that. And so they actually had to pull it back off the market. It was unavailable for a couple of years. And now they've done what they needed to do to hopefully stabilize it, and it's been available.

So for a lot of reasons, people mostly use the -- for those reasons, the WHO stuff is the one that's been more used.

DR. BADEN: Will this standard, assuming there were adequate supply of standard, would that allow comparability of results across laboratories? Or are there intrinsic limitations to the standards being used that way?

DR. COOK: Well, so we use these standards once or twice a year. That's all you really get. And so what you have to do is take your standard, compare it to whatever you're going to use on a daily basis. As I described, some people don't use it very often. Some people use it every single day.

And so we have to have a separate process in place if we're going to make our own standard. And so there are issues with that. The commercial labs do the same thing. They make a calibrator. They put it in their assay. It may or may not run exactly the same in anyone else's assay. So there are some inherent limitations to that.

DR. PETTI: We have several people who have questions, so we'll first start with Dr. Beavis, then Mr. Bracco, Dr. Kotton, Dr. Blumberg, and then Dr. Schaenman.

DR. BEAVIS: Thank you. This is Kathleen Beavis.

And I just had a follow -- I had a comment to your question about oversight of LDTs. And you're right; at this point, you know, the FDA does not have a role in that, but I will tell you that as a laboratory director under CLIA, every laboratory director has to approve a verification or validation before it's done in his or her laboratory.

I will also say that there's proficiency testing that's part of that, and that also helps. So, you know, it's not exactly the Wild West. Okay, there is some oversight. But you're right, it's not centralized.

DR. BADEN: Understood.

DR. GITTERMAN: If I could just clarify just what I say. Do we have a lawyer here?

Because I don't want to say the wrong thing. Technically, FDA does have oversight. It is not that FDA has basically waived its oversight over laboratory-developed tests; it's just not enforced. I would hate the Committee to say, oh my goodness, how did these escape regulation? It's not that they escaped regulations; it's just the way the regulations are enforced at this time.

DR. BADEN: I think that's what I was getting at.

DR. GITTERMAN: Yeah. You're 100% correct. But I don't want people to say, my God, we have to do something right now about the regulations. No, they are regulated. How they're regulated is a fair question, and the enforcement of those regulations is a fair question. So if there were a wildly mis-performing LDT that we were aware of, etc., of course we'd take action.

MR. BRACCO: This is Dan Bracco.

I actually had two comments. First, on the lab-developed tests, the current FDA thinking -- you're right, it's still a draft guidance. But the current FDA thinking is that any Class III laboratory test would be immediately put in front of the FDA if these regulations did come into play. So that's actually, you know, one thing you need to think about with these Class III designates.

DR. GITTERMAN: Right. If I could interrupt, and I mean this very sincerely, I would not speculate.

MR. BRACCO: Okay. Well, I'm just leading --

DR. GITTERMAN: I'm not -- because we shouldn't be spreading misinformation.

MR. BRACCO: Correct.

DR. GITTERMAN: None of us have this around the table. And I'm being serious. We should not be speculating and asking the Committee to make decisions on what may or may not happen. Again, I would never make this personal, but none of us in the room know

that. It's been several years now since those draft regulations. Everybody recognizes the importance of these. And what was published, one could say it was almost a "tryable-on." What will happen, if anything happens, please, I would not speculate on that. And when you say current thinking, none of us know exactly what the current thinking is.

MR. BRACCO: Well, that is published information, correct?

DR. GITTERMAN: No.

MR. BRACCO: The draft guidance?

DR. GITTERMAN: The draft guidance is published.

MR. BRACCO: It's published.

DR. GITTERMAN: And that's true, but again, it's draft.

MR. BRACCO: Okay.

DR. GITTERMAN: If you were to say what's in the draft guidance 2 years ago that has no regulatory standing, that would be fair. But again, I put --

MR. BRACCO: Okay.

DR. GITTERMAN: Thank you.

MR. BRACCO: So the second part of my LDT comment was that it really has nothing to do with this particular downclassification discussion because a lab-developed test, right now, a lab can do what they want in their laboratory. So if it's a Class I, a Class II, or a Class III, it does not matter to that laboratory. So in this type of discussion, it's probably not relevant.

The other thing I wanted to comment on, Dr. Gitterman, was your comment on the annual reports. I think you glossed over that maybe a little too lightly. The annual reports are required for all Class III medical devices. And although they are a considerable burden for industry, they're actually very useful for the FDA in that they keep the FDA continually updated on any aspects of the test that's out there.

So, for instance, they can look at all the adverse events that occurred for that particular test. Anything new in the literature, FDA will get a chance to review that on a yearly basis. So that's one of the benefits of having a Class III device is that, like I said, although a burden for the manufacturer, it keeps FDA current in terms of that particular assay or medical device, whatever it is.

DR. GITTERMAN: We could switch seats. We could switch seats, but we have other ways of staying abreast, but that's -- I couldn't agree more.

DR. PETTI: Dr. Blumberg.

DR. BLUMBERG: I just have a question. In terms of setting standards, so when you develop an assay, in deciding what the standard's going to be, what is the FDA's role in helping to determine the standard? And if that's something where if this test is downclassified to II, that as one of the special considerations, we could say, there needs to be the use of specific standards.

DR. GITTERMAN: Let me -- one is, of course, we could and, you know, FDA participates in the standards process often, you know. But if I interpreted your question right, and I apologize, we could certainly say what, as Dr. Whitaker said, what the total allowable error is, what the comparison would be, what the acceptable linearity would be, issues like that.

By standards, we could define what would be acceptable, in the same way we have very specific clinical guidance, and CLSI publishes extensive guidance regarding what would be acceptable deviations or not.

But when you're talking about -- if you're talking about which standard we should accept --

DR. BLUMBERG: Yeah. I mean, I guess I'm trying to say standardization across labs. Would like -- so this whole issue of a international standard or something like that, can that

be a requirement or --

DR. GITTERMAN: Yes.

DR. BLUMBERG: -- something that that?

DR. GITTERMAN: Yes. It certainly could be --

DR. BLUMBERG: I mean, because I think that's one of the biggest issues with CMV testing is trying to interpret the assay across labs. And, you know, there's still a lot of issues with it, but if there's no ability to clarify what the, you know, ground game's going to be, then you don't --

DR. GITTERMAN: That's exactly right. And it's a fair -- and you know, it's a fair question. Again, certainly, Dr. Cook could comment far better than I am, but even with a standard, that doesn't ensure perfect commutability. But one could argue, or one could reasonably discuss, as I think she showed, so the seminal slide, what happens when we introduce a standard, even if it's not really a standard, even if it's sort of a consensus value. Look how dramatically the variability across labs can decrease.

And again, one could suggest that even if perhaps they're not perfectly commutable, what the acceptable differences are. In clinical study, what are the areas that need to be studied to make sure? I mean, one could suggest that, well, does 50- to 60,000 make much difference? Probably not. But at certain ranges where differences might be significant, or what's a change in values like -- and, you know, as one might define in reproducibility studies or repeatability studies, that one might consider acceptable.

Again, I hate to say it, when the first CD4 cells, you know, patient comes up high, the first thing we tell them that is they're going to regress to the mean next time because the viral load's suppressed and ignore it. That's why we don't even measure them half the time anymore.

But again, in CMV being measured acutely, where you have suspicion, that

difference is critical. And as, I think, Dr. Limaye had said, you know, again, in the setting where somebody is not reacting as expected to valgan or ganciclovir, the differences make, you know, whether you're going to go out to do, use non-CLIA tests for UL97 or non-approved tests for that is something to be considered.

So these are all, you know, all fair questions to say. But, you know, again, the examples -- we could do very well in defining perhaps what the requirements would be around some of these parameters. We have a lot of experience, you know, deciding how, you know, what's acceptable error, how to measure error, you know, how to do your various regressions, etc.

But again, there is going to be some error. I think Dr. Whitaker had a very good slide saying, should we even say that you must use the same test? Now, that may not even be practiced now, but that's something that could be considered. And the reason everybody wants to do that, I would suspect all of you prefer to have, you know, them all measured in your labs for reasons that were raised before. People can't come back. They may not be reliable. There is certainly a time difference. These are send-outs. Transport of specimens is always an issue. You know, they may be batched. It's, you know, a lot of clinical concerns as more tests get out there.

Did that -- did I answer your question? I said a lot. I'm not sure I answered it.

DR. BLUMBERG: I think you did, thank you.

DR. PETTI: So Dr. Schaenman, then Dr. Meyer and Dr. Hayden.

DR. SCHAENMAN: Joanna Schaenman, UCLA.

I have a two-part question for Dr. Gitterman. The first one, I think, is sort of related to the issues that Dr. Blumberg just brought up. I think that you've explained well to us the safeguards that are inherently within the Class III classification in terms of the premarket approval process and the requirement for annual reports.

I guess my question is if we were to declassify, could we use the special controls if we specifically created a CMV-specific set of special controls that might be able to address some of the current issues, the current problems that exist within the standard of care for CMV testing? And might we improve test performance and standardization sort of by crafting, if you understand the question, some --

DR. GITTERMAN: I do.

DR. SCHAENMAN: -- CMV-specific controls as opposed to the --

DR. GITTERMAN: That is --

DR. SCHAENMAN: -- the generic Class III?

DR. GITTERMAN: -- exactly why you're here. I want to reiterate that. But it's -- again, you know, we could come off things off the top of our heads, but again -- and you know, really, I can't say how pleased we are with the group around the table. This is a world-class expertise. What do we need to make sure of? What would be a mistake if we don't do that? I mean, these go into regulations. And Dr. Evantash is going to sit there and say that's in the reg and that's not in the reg.

You know, can this be done, yes or no? I mean, are people comfortable having the absences of annual reports, having the ability to tailor it more specifically? Or as a group, do you think that one could write special controls, to say this would be pretty encompassing such that yes, we think, if companies do all this, and the devices address these issues, we can reasonably say we're safe to have more of them on the market -- well, possibly more on the market and possibly expose patients to variabilities.

You know, I think, Hologic, I think Dr. Limaye, I think people have brought this -- but the answer is yes, that's exactly what you want to do.

DR. SCHAENMAN: All right. That's helpful.

DR. GITTERMAN: What we want, what we would like you to do. And please don't

use declassify. Reclassify.

DR. SCHAENMAN: Sorry. Downclassify.

DR. GITTERMAN: Reclassify.

DR. SCHAENMAN: Reclassify.

DR. GITTERMAN: I know, a slip of the tongue.

DR. SCHAENMAN: I apologize. I apologize.

DR. GITTERMAN: No.

DR. SCHAENMAN: And I guess, in a related question, I think the two presentations from University of Washington brought up the fact that CMV is an international problem. You know, we're looking at standards from Karolinska. Per Ljungman is a leader in the field. We're talking about the WHO international standards, which, I think, brings up the question of how do other countries with major transplant centers classify the currently available test? Because I believe they're available worldwide.

DR. GITTERMAN: Apples and oranges. The system, you know, it's just as example, in the EU is very different and actually is evolving. They have a number of proposals to change their assays. So I don't think it would be fair to directly compare it. I will certainly say, though, that people will look to the work of this Committee, as will across the world, to say these are reasonable control -- these may or may not be reasonable controls that one could put into developing such an assay.

And I also believe, too, that much of what we say this morning is going to be translatable to this afternoon, although certainly, I think, just people realize that's a different kettle of fish. So we have to do a better job. We should say, you know, we should have a statement there, what are you supposed to do? So you earned that $25. Or is it you have to pay $25? I can't recall.

DR. HAYDEN: Hi. Randy Hayden.

I guess it was just a comment. Just in listening to some of what people are saying, it seems like there is really two issues. One is Class II to Class III, and one is trying to improve CMV testing. And I'm not sure -- I mean, they're not always the same question. I think a lot of the things that are being talked about aren't necessarily embodied in the current assays on the market, to the extent that they might be, irrespective of whether they've gone through the Class III regulatory process.

And so, you know, I guess just a comment to that, that, you know, all the comments are good, and improving standardization, commutability, use of international standards, and so forth we need, irrespective of whether or not it's reclassified, and probably maybe can be done irrespective of whether or not it's reclassified.

DR. GITTERMAN: And I think that's fair. I think, as Dr. Whitaker clearly said, it's safety and effectiveness; we all know perfection is the enemy of the good. But under a Class II paradigm with, let's say, imperfect assays, can we write special controls that mean they can be used safely? Perfection -- you know, we realize no assay is ever going to be perfect. And again, we get recalls whether they're Class III or Class II. You know, assays go bad as well as people do.

But the fact is can we do enough -- can there be the presence of special controls that we feel really pretty comfortable without being able to review everything and specify what a manufacturer should do, instead of again, FDA looking at each individual assay applying, to define what the properties of it is, how it should be doing, doing this on an evolving basis as more knowledge becomes available, etc.?

And what you said, I completely agree. We are not going to solve every problem for CMV that -- well, perhaps we might, but I suspect not.

DR. MEYER: Dan Meyer, and another question for Dr. Gitterman.

DR. GITTERMAN: Wait. All the questions don't have to go to me. I mean, that -- is

that the task of the Committee, Dr. Petti?

DR. PETTI: No.

DR. MEYER: That's right.

DR. GITTERMAN: No.

DR. MEYER: Okay. Just to the FDA then. As we're charged with, you know, potentially developing these special controls, historically, are there some situations where Class II tests or laboratory-developed tests or other assays have been reclassified to Class III, and what were the issues that we may want to avoid?

DR. GITTERMAN: In our division, and I look, you know, I look around the room, I do not believe Class II to Class III has occurred. We have recently had Class I to Class II, and that was the rapid flu assays. I don't believe, to my knowledge, that there has been a Class II to Class III upclassification. I would have to think. Wait.

(Off microphone remarks.)

DR. GITTERMAN: Okay. I have been confirmed that I'm correct on this occasion. But let me ask, why do you ask?

DR. MEYER: Well, basically, if we develop a special control to reclassify it from Class III to Class II, for accuracy or some precision of testing, I wanted to see if there were some prior lab studies that those special controls weren't specific enough or just strong enough to keep that laboratory study in that classification.

DR. GITTERMAN: Well, two things. One is there is a transcript, so we'll know who to blame, and we will make certain to invite you back.

The interesting thing, and just as an aside, we had one of our reclassification meetings a couple of years ago. We actually were able to have a couple of people come back -- actually, one was still on the Committee, I'm not sure how that happened -- who had made an original decision that we were changing at that point, and that was fairly

interesting. So we had to remember every single thing they said. But we're not in a position of prosecuting them. Back 10 years ago, you said -- but no, it's not common that we're aware of. And hopefully it's not common because there are good special controls.

DR. PETTI: Dr. Chou, Dr. La Hoz, and then Dr. Green.

DR. CHOU: Sunwen Chou.

So as somebody who like grows CMV in the lab for a living, I just wanted to offer perspective on special controls, because it seems like a big part of the decision to classify as Class II is are these special controls available that everybody believes is adequately developed? This WHO international standard falls short and is a sort of a work in progress that needs further development.

I would be very loath to specify the current WHO standard as the special control or the principal special control and probably word it as something that the FDA sees fit, in light of our current technology or what. But some of the shortcomings of the WHO standard is that it's actually a cell culture base preparation of a single CMV strain, Merlin.

And, you know, inherent in all culture-based things, every batch is really different in terms of its exact DNA composition, the fragment length of the DNA that's represented. Those things can vary according to how you've grown and handled the culture, and so on, so forth. And by its nature as a culture, is pretty much, by definition, a limited supply.

I think the day will come when we will need to go to molecular standards, that the controls are, in fact, you know, plasmid-based or BAC-based DNA. And even then, the question comes up of what strains should be incorporated and what average length of the fragment should be.

And then the issue of commutability, that is, if you calibrate to some accepted standard, does that represent what's in plasma specimens, which is now widely viewed to be really bits and pieces of possibly even waste DNA from CMV replication? And how do we

properly, you know, mimic that in a standard?

And so I would advocate for special controls to include the requirement, not only for calibration to some type of accepted standard, but the need to take several dozen clinical specimens through parallel testing in several assay platforms, including those that are FDA approved.

DR. LA HOZ: Ricardo La Hoz, UT Southwestern.

So as we set sails to come up with special controls, I would also like to give the clinical aspect of the result. And I'm not going to state something that's new to any of the Panelists, but these results need to be interpreted in a context. So who is the patient? What type of transplant did they receive?

Core stem cell transplant is not the same as other types of stem cell transplant. The lung transplant is not the same as a kidney transplant. They're different serology, so -- and I think, as some of the presenters pointed out, you know, the kinetics of the changes in the test and so many variables.

So beyond the single result of the test is also the person that interprets the result, and how do they assess their clinical risk on what's the significant of that result? So I guess what I propose is who interprets the result of the test is also important in determining whether there is going to be a risk to that patient, whether for undertreatment, overtreatment, and I think that's also an important factor to include on those special controls.

DR. GITTERMAN: For the one is I think you will probably find agreement around the table, because several people have informally mentioned that. I would say that, as Dr. Whitaker put it, we can put special controls in labeling. Labelings may have, you know, may have to do that.

But again, as people -- you know, as people recognize, you know, laboratories will

follow the labeling, but clinicians rarely see a package label and rarely do it. So the translation of something we might see in labeling, you have to be convinced that laboratories that perform it will make sure that, in fact, these -- that there is processes in place. But we can put things in the labeling. Whether people believe that, in fact, is enough to mitigate the risk certainly is a, you know, is a fair question.

I mean, a lot of -- I would certainly like to take a quick poll about how many of the clinicians in the room, not the laboratorians, have actually ever read a package insert for any of the tests they use.

Okay. People are showing off. Okay.

But no. I mean, I would say we don't have a house staff that has ever -- doesn't even know who has run the test, much less whether it's a send-out. The only questions they ever ask is there's a little comment on the bottom that says this has not been approved by FDA but has been validated by CLIA. And they say what the heck does that mean? And, you know, the chief resident will say just ignore it.

So, but no, it's a very good point. Absolutely.

DR. PETTI: Dr. Green, Dr. Welch, and then Mr. Simon.

DR. GREEN: So I have a comment and a question. The comment, I think, is well known to the Panel, but I'll just say it again, is in the studies that were done looking at comparability of results at many different centers, as I recall, when they looked at many different centers using a Class III FDA-approved device, there was a fairly significant variability from center to center using a Class III FDA-approved device.

My question -- and I don't know if FDA can clarify this or not -- is I think part of the reason we're thinking about this is that there's a perceived barrier for industry to bring new devices to market so that we could perhaps move away from laboratory-developed tests. And so my question is does FDA have a sense, is the barrier to bringing these devices to

market, one, the getting all of the analytical performance measures, as defined on Slide 9 in the presentation that we had from FDA, or is it getting the -- doing the sort of longitudinal, clinical studies, which one of the two products was able to leverage together with a clinical trial and therefore save money, but others may not do it.

So I think, as I think about it, it would be very helpful for me to understand, what is the real barrier? Because in our developing sort of our guidance controls, if it's just the clinical trials and we have a comparator Class III device to use, we might be able to overcome that while still maintaining mandates to having the analytical performance measure requirements in place as part of those special rules in place.

DR. GITTERMAN: Let me parse this. The first thing I have to respond to, because I didn't catch all of it, so I apologize, but for longitudinal studies, those mean different things to different people. And perhaps we can clarify that. One is clinical effectiveness versus longitudinal samples or longitudinal specimens. Again, one could -- clinical effectiveness, I think, is clear. I don't think anybody is debating the fact that somebody's going to have to go back and expose patients to risk to say we're not sure if this works. I mean, clearly there's questions about what the right thresholds are, risk-benefit for intervention. But I don't think anybody is going to debate that.

Now, longitudinal studies versus cross-sectional samples, one could conceivably argue that if we had a large variety of specimens, and we tried to get patients within certain levels that we thought were within cutoffs or not, or supplemented those by contrived specimens, we could capture everything we needed to know about the properties of a test.

Another way of doing that, that would -- or another equally important, one might suggest, is following individual patients over time. So, again, you have centers which somebody does have therapy initiated, we'd like to see how this device responds to therapy, and especially as they get near the level of quantitation or level of detection, very

low, do they bounce around it? How well do they do?

I mean, there's a poster at IDWeek that said, Jesus, R-squares were tremendous, but if we really look in that really narrow box between 0 and 200, or actually even 400, that's where the tests bounce around. And some are a little more quantitative. And anybody who followed the debate about HCV and cure, depending on which assay you used, and bouncing around, you know, can testify that a lot of people would like to know that. And things like that might affect duration of therapy, who's treated, etc.

So those are two points. Now, this third point is when you talked about perceived barriers. There are many -- and Dr. Bracco, being the other side, no doubt, can comment far better, but not only is it a cost, but the amount of documentation are substantially greater for the cost to a PMA, without going into details, and the cost over the lifecycle of the device, etc., is very substantial. It's very different for a company that's adding it to a platform than, you know, than a company which doesn't have a platform.

But it would be fair to say that there would not be any manufacturer in the room who would not substantially believe that the differences are substantial enough to -- strong, and all things being equal, would not very, very much want a 510(k), unless of course, you're on the market, in which case it's about, you know, perceived barriers to competition. And, you know, you've put all the effort in, so that's -- you know, there's different motivations. And some of these sponsors may legitimately feel that, from what they know of their device, that they are putting other people at risk.

One thing, too, and again, I would speak to the laboratorians, including Dr. Cook, the 510(k) paradigm, you know, demands a lot. You know, nobody -- everybody wants to have confidence in the devices and the tests that are used to treat patients. And it's not as if the 510(k) paradigm means, oh, laboratories can do some of this, some of that, and it's gone. I mean, the obligations of a manufacturer, a device manufacturer, go way beyond just

developing the test. It's adverse events. It's having quality systems. It's a lot of things that were discussed in this guidance.

And reclassifying something as a 510(k) does not mean, you know, the doors are open and everybody could come in. It's -- you know, there are large clinical laboratories, not even on the order of a, you know, a Quest or a LabCorp or, you know, other very, very large laboratories that, you know, find it very challenging that sometimes have to employ a full-time, you know, regulatory person just to do some of the things they do. It's not trivial.

So, you know, when you specify special controls, really, the issue should be solely patients. But it's what we feel would be necessary and sufficient to assure the safety of these devices in use.

We could talk afterwards about this paper that shows a lot of FDA variability. All these devices will have variability, but the amount and the reproducibility and repeatability of FDA devices, I think, easily is superior, if not comparable. And there are some exceptionally good LDTs. Nobody would deny that. But certainly it's far better than the average LDTs in the publications. I think, as the standards or means of assuring -- reducing variability across labs has, you know, been done by standards, in fact, that's always resulted in this.

And you may want to comment, Dr. Beavis, on whether that, in fact, is part of CLIA regulations, which it's not. You know, the idea of how much it measures against the standard, how accurately it measures in that regard, you know, may not be evaluated by other mechanisms.

I'm giving very long-winded answers. I hope I actually am addressing the questions. I get lost half the time. Okay. Is the FDA hour done?

(Laughter.)

DR. WELCH: David Welch, Dallas, Texas.

Similar to Dr. La Hoz's comments, I wanted to ask about the special control of interpretation of results, and particularly in the context of the expertise of personnel. Is it in the purview of the FDA to go into that? Is that an element of interpretation of results, the personnel expertise of --

DR. GITTERMAN: We could put something like that in labeling, clearly. These results should be interpreted solely by individuals familiar with the clinical care of patients undergoing transplantation. Now, who's qualified to do that is certainly, you know, debatable. No, we could put that in labeling. It has appeared before. That is not a problem. One would hope the individuals would consider malpractice if they're managing patients in this. But, you know, it does happen. But, in fact, that can be put in the labeling.

Because again, if there was the fear that somebody might come to an ER, which in fact, is happening, and we all know of patients that go to ERs or are cared by non-transplant physicians who miss the boat. And we're all, you know, we're all aware of that. But, in fact, as far as our, you know, our ability, yes, we can put in the -- we could put as specific special control as labeling, that the interpretation of these results must be done by a clinician or a laboratorian experienced in the interpretation of these results.

DR. WELCH: I just thought that that would be important to consider, because there are laboratories that have little or no oversight, on a day-to-day basis, by professional directors.

DR. GITTERMAN: Yeah.

DR. WELCH: And so for those -- in those cases, I think they can tend to get into more trouble than other laboratories.

DR. GITTERMAN: I would completely agree with you, and I would suspect that the laboratorians around the table would say, to me, a laboratory has no business offering that test. But that's just my personal opinion. Oh, I'm getting a nod from Dr. Beavis. Let the

minutes reflect, Dr. Beavis agrees.

MR. SIMON: Tom Simon.

I hope I can say this correctly. If I heard one of the speakers say that patient access is restricted because of the Class III status, if that's correct, that's a risk to the patient already. Number two, if the CMV viral load assay is the only means of detecting CMV -- sorry, CMV, that's a risk also to the patient. If that's the case, why wouldn't we reclassify to a Class II? Because in itself, the risk, because of the expertise and experience in this room, we could come up with special controls for the reclassification that, in essence, then, would open for more patients to get the test. And I think that's it.

DR. GITTERMAN: I think that that's a fair comment. I would again defer -- I practice in an open area. We have no problem getting access to viral loads, and adequate -- I think there's unique situations where, you know, preemptive therapy, where getting it in real-time is more critical than not. And again, you know, people who treat -- there's, you know, resolution of clinical symptoms that the real-time may not be a key piece.

And again, I hate to say it, most transplant patients are usually reliable. Very often, if they're not getting tested, I don't think it's a question of access as much as compliance. But I certainly would welcome -- and I think that's one of the reasons we're very lucky, people in the room to question it. I'm not sure I would agree with your premise that it's a difficult thing to access. But again, transplant numbers are increasing. And that may be a relatively new concern.

I might -- and again, I'm looking across at Dr. Kotton, or anyone can tackle it there clearly -- and as Dr. Whitaker suggested, I don't think there's a transplant center in the world who would not prefer you get retested by their assay, whether it's FDA cleared or -- FDA approved or not.

Please.

DR. PETTI: Dr. Kotton.

DR. KOTTON: Camille Kotton. So it actually -- this is a huge issue for us. It's not an issue when we have inpatients and we're doing the testing on a repetitive basis within our own laboratory. But as somebody who practices in Boston, our catchment area goes all through New England into New York State. And on a very regular basis -- I would say this is either a daily to several times a week event, I have people who undergo testing at an outside laboratory.

The testing is either sent incorrectly and interpreted by the laboratory. Maybe they don't have viral load testing, so they do things like serum IgG that's useless. That delays care of the patient and compromises the safety and outcomes for the patient. And/or they do qualitative testing or quantitative testing. And I suspect that I'm speaking for most everybody at the table, that you get erroneous testing results, and it's unclear what it means to that individual patient.

And so I do think that that's a very regular issue for us. Another huge issue, and something that I would really like included in the special controls, if we do downclass this to a Class II, would be the specimen type, because it's interesting that you said that this is really just for plasma, but across the board, we see a lot of different specimen types tested. And even worse, it's not always obvious what they're testing.

And I personally often will call the laboratory and say what color -- what tube did you send? Was this a lavender top tube? You know, what was actually sent? And, you know, often, even when I call, I can't get the right answer. So there's a lot of chaos out there. And it would be great to have, as has been the refrain, better standardization. And that would really allow me to take better care of patients.

DR. GITTERMAN: Yeah. Just as kind of the second point, and I say this with a complete smile on my face, wrong day. We actually had a very large meeting yesterday on

semantic interoperability. Gil Alterovitz from Boston Children's was there. But on trying to address this, because that issue, I think, goes beyond -- you know, goes across many tests.

Actually, FDA's very involved in this issue of assuring semantic interoperability to allow decision support. So that's actually a great interest. How to assure this, and how -- you know, again, manufacturers can know to put this in messages, etc., etc. But it is a real concern, but maybe somewhat separate from this. But the point that things can be clearly labeled, absolutely.

And to the case, I think, somebody made before, the importance of using alternative specimens. Now, again, I think it has to be clear what you're measuring. If you're talking about measuring CSF, I believe was brought up earlier, again, that's a different analyte and is very, very different than, say, perhaps using an alternative. It's a different matrix. The analyte, of course, is the same. And, you know, that requires a lot more -- yeah.

And again, whole blood, recognizing there is clear measurement differences, and you can't relate from -- you know, it's not -- it doesn't transfer, or -- I'm blanking the right word. But the fact is they would need more studies. Your point is very well taken.

MR. BRACCO: I just want to make a comment, too, about -- oh, Dan Bracco, by the way.

I want to make a comment about the special controls and the whole process with FDA. With a Class III medical device, FDA basically starts with a clean slate. And they use their current thinking, their current knowledge base, which continually increases. And they'll evaluate that device or test from scratch, so to speak. And all the things you talked about earlier, Dr. Gitterman, today, are included in that evaluation.

In the Class II process, even with special controls, the FDA will most likely review your device or test versus a predicate, something that's already in the market. And what happens all the time is the more and more tests that are in the market, the more and more

you see some variability. And that variability oftentimes builds up because FDA has to just compare you to that predicate device that you've put in your submission.

So it's important to think about that in downclassifying this device, that there is the potential for more variability because you can choose any device out there, or test, as long as it has the same intended use and same technological characteristics, or with different technological characteristics as long as they don't raise new questions of safety and effectiveness.

DR. GITTERMAN: No. And I have to say, I -- that's a really important point because essentially we could use -- the drugs model might be a better model. When you have -- so these essentially are non-inferiority studies. They're not -- you know, you can't be, never be equal. You could be similar to, within a certain range.

And again, what -- there are many terms to use. Drift is one term, but again, if devices successively get worse, then in fact, as you compare yourself to worse and worse devices, you know, as happened in drugs, when you have -- you know, when you have a low performer, and then everybody compares themselves to the lowest performer, you end up with a device that may not have any efficacy at all.

Hopefully -- and I completely agree with you, that with the presence -- and I very much await, you know, the deliberations subsequently -- can there be controls that actually mitigate that? That is the -- what we do not want is a race to the bottom, where people pick the worst possible test, show that they're comparable. Again, when you say, comparable, those are non-inferiority margins, which mean you can be worse, you're just not that much worse than the existing standard, such that -- I'm going to use drift, but there's -- drift is used differently.

What is the term I'm thinking of? Everybody knows it, where you keep successively comparing yourself down, so the ultimate performance is far, far worse than the original

innovator. Okay. I will remember it over lunch, I'm sure, and come back this afternoon and say it.

But the fact is, you want to have special controls. And presumably that's what a standard would do. But Mr. Bracco is absolutely correct. That is a concern. And I would also say, too, of course, we don't start with a blind slate. But it does. It allows us to, in the evaluation of a new device, take the most recent evidence, the recent changes, and make sure that that device is approved to the most rigorous and most important current recommendations.

And hopefully, that will reflect itself in the performance. Why is one assay better than the other? And people know it. And as assays -- you know, as the ability to test different things improves, that, in fact, would be reflected in the devices. It's not obviously a wholly blank slate, because we do have previous experience, but it does give us a lot of ability to keep up with technology, with standards, what we learn clinically, as Mr. Bracco said, what we learn from adverse events, and incorporate that into the new devices.

DR. HAYDEN: I'm trying to remember what I was going to say. I just wanted to mention -- go back to the question of access, I guess, because I feel like, again, it's not just an absolute question of access, but it's a question of timely access and local access and the fact that, with only a couple of manufacturers in the current climate, give or take, being able to sort of get a product out, you know, it basically reduces choice.

And it means that we have essentially -- typically, the first assays that are out there, if there's only one or two, are targeted at very high throughput laboratories. They're not cost effective to have on-site for most places. So you end up with, you know, both a cost and a time to result barrier that might be alleviated somewhat by having a greater access, greater practical access through the approval process.

Then too, I think also, even amongst the manufacturers that have devices out there,

again, they tend to maybe go for the compartment or the matrix that is, you know, maybe the biggest, but you know, there's still a lot of people testing in whole blood. So I think that's another form of access that's limited right now.

DR. GITTERMAN: I would, if I could, just make one caution, that there are two approved assays out there right now. One could Google, one could go to ClinicalTrials.gov. One could go to industry meetings to see whether there are other ongoing clinical trials, other devices.

I appreciate that, but again, this is a moment in time, and it doesn't mean this will always be the way. Yes, as a committee, you could say this, there are challenges to the PMA over the 510(k) process, and unequivocally, you'd be correct. It's a fact that as of November 9th, there are only two approved products. But I would not suggest that that would be -- unless the Committee takes a certain action -- this would be forever the only two devices on the market.

And I would just say that there are resources available to see if other things are under development that we cannot comment on that issue.

DR. PEREIRA: Marcus Pereira from Columbia University.

Just wanted to continue the discussion on the existing standards. And actually, my question is someone other than Dr. Gitterman, and maybe actually as many people who would like to answer it.

I was disturbed or perturbed but not surprised that Dr. Chou had talked about sort of the inadequacies of the WHO standard, or the NIST standard as well, and proposing sort of a panel of clinical specimens that could parallel and could be used as perhaps a new standard or an adjunctive standard. That clearly seems like the creation of a new standard. And who would be -- sort of what are the logistical aspects of that? Who would create that, and how would that be assured, the sort of maintenance of standardization? It seems

awfully complex to create a new standard for this.

DR. CHOU: Yeah, so I think, although ideal, you know, specimens, controlled specimens made from actual patient plasma have huge logistical problems with getting enough of the quantity and to be able to preserve it and have it stable for use over a prolonged time. So although it's preferred, I just don't see how it can happen. And I think that's been widely recognized in the clinical testing community. You know, how we get around that is very tough.

I mean, I had thought of some crazy ideas like can we go around and, you know, go recruit people who have multimillion-copy loads and say would you donate, you know, for the public health good, and we'll make, you know, dilutions from that. But, you know, any crazy ideas like that would still not solve the long-term, you know, need for a stable control.

DR. HAYDEN: So, you know, I think that the current international standards are certainly far from perfect and are a work in progress, but I think that they are a standard. And I think that it's -- to me -- well, part -- there's two issues. One is that the specials that -- controls that are in place, and the demands that we make of international standards do have to do with the labeling that we put on this. And if the labeling surrounds more a demand for being able to follow dynamic trends, while still demanding special controls to standardize, to the extent possible, given the current state of the art in standardization, you know, that might be where we want to start. And then work through the current framework of groups doing international standards, either NIST or WHO, to improve those standards, you know, work with the manufacturers to improve commutability, vis-à-vis the standards.

But at the same time, you know, that doesn't need to be a hard barrier because that imperfection exists whether or not this is Class II or Class III. So, I mean, I think the faults in the current international standards are very well described. But I also think that I don't

know that I would go to sort of creating an entirely new animal as much as take the animal that we have and maybe take the animal's inventor and work with them to improve it over time.

DR. GITTERMAN: Just as a thought experiment, and hopefully you will discuss this later, because the question is can you write something down without, again, you know, using -- as things evolve. But let's say there's only one device out there, and there wasn't a standard. Or let's say there's two under development. How do you address commutability in something like that?

Now, there are -- as Dr. Whitaker had suggested earlier, the method comparison studies, you can include another FDA-approved/cleared assay. Or you could, you know, you could write things down in such a way, and I would urge you to consider that, because you write clearly -- and I think this has been discussed at length internally, that there are issues with the standards and, you know, even more problematic to add an editorial opinion this afternoon.

So let's say the standard -- let's say there wasn't a standard. Would this always, by definition, have to be a PMA? Or what alternative controls could we write to minimize variability that we think would be acceptable? We could say yes, you have to use an internal standard, or you have to use an FDA-cleared assay. Now, again, that would allow -- I know I'm using the word "drift" wrong, and again, what if one assay changes and one assay goes out of business? Lord knows, you know, there's a lot of difficulties when you start specifying this.

But again, we welcome discussion on this, this afternoon. What is it that we can write down specifically, and say if you do these things, we're going to feel fairly comfortable that, in fact, you know, your device is safe and effective as marketed?

DR. BEAVIS: So this is Kathleen Beavis.

And again, you know, this is not ready, wordsmithed or anything, but it reminds me of some of the discussions we had about the upclassification for the rapid flu devices, because as I remember, some of the special conditions put in there were -- and I don't remember, you know, the things that were suggested exactly, but it was, you know, whether it was annual or every other couple of years that manufacturers had to show that they were working against the viruses currently circulating. And again, something like that could be put in.

DR. GITTERMAN: Absolutely. And I think Dr. Whitaker, with some discussion with Dr. Beavis, exactly mentioned that. Now, I think flu is the obvious case because, you know, there, there's true drift that, you know, that you're basically trying to show that the virus is -- you know, that the test captures new viruses, etc., that it's accurate for the market. But the fact is that that is true.

In the same way, again, I think, as Dr. Whitaker clearly pointed out, if you could come up with a special control that you think would maintain the safety over time, there may be different issues with reactivity/inclusivity, you know, as different -- you know, perhaps there's a -- you know, again, it's not quite the issue with CMV. But as emergence of different strains, that's a concern.

But again, given it's a quantitative test, and given not only -- you know, again, I think, as was well mentioned earlier, there's very different populations, you know, very different, you know, different recommendations -- there's not quite thresholds as yet, and of course, they're very patient specific, that some type of requirements, postmarket, and say you need to do this X years. And as also was pointed out is standards change, and you know, a requirement that manufacturers then, you know, compare themselves against a standard, etc., etc., absolutely we would welcome that kind of input. Absolutely.

DR. BEAVIS: Yeah, this is Kathleen.

And I think that's our challenge this afternoon is how to come up with something that will allow, you know, the evolution. You know, I remember the one manufacturer talk this, you know, this morning, that said, things should be compared to the first WHO standard. And no, I mean, that wouldn't be appropriate. I really do think things are going to be evolved, and we have to figure out the wording to allow that.

DR. GITTERMAN: I'd say that this is not a trivial problem. I mean, you know, again, these are critically ill patients, and sometimes, and that -- you know, we are very, very grateful the time you spend thinking about it. And I'd be very grateful to not have any additional questions.

DR. BLUMBERG: I had one comment on this, and then one other comment to veer in a slightly different direction. In terms of this, just from a technical standpoint, there, in the -- one of the prior presentations, sort of one of the addendum slides talked about interfering substances and standardization, or just the assay variability with interfering substances.

And I have to say, that was news to me. I didn't -- I was not aware of interfering substances affecting this in quite the way, with quite the broad list of interfering substances, most of which are medications used in transplantation. And I don't know if somebody here can comment on whether or not, when doing standardization of assays, and someone, maybe you would know whether or not, with the WHO standard, that those sorts of issues were addressed. That was my question, and then I have another one, but --

DR. PETTI: Yes. I'd like to bring Linda Cook back to the podium and perhaps share her experience with interfering substances and other analytical performance issues.

DR. COOK: Directly about the WHO, it doesn't address anything related to interfering substances. There is a tremendous list of interfering substances that is in the literature that interferes with PCR. There are a few things that interfere with extractions.

And hence, we need those extraction controls that I was talking about.

But I was also surprised. We probably see -- we are running about 75 to 100 CMVs a day, 6 days a week, mostly transplant monitoring. And we probably see one or two samples a month that have inhibition in such a way that we can't get a result. So it's a fairly, what I would say, a minor issue. But I think that's one of the reasons why, when you do these cross-comparisons, you have to do a lot of patient specimens because what might cause interference in one assay may or may not cause interference in another assay.

But, in general, we don't have a problem. A few years ago, we did a specific study on digital PCR, to try to figure out whether or not it was less susceptible to interference than real-time PCR. And the idea there is that you're compartmentalizing whatever you might have in the sample into all these little drops, and then you're doing an individual little PCR in maybe 20,000 wells. So large molecule inhibitors, like heparin, for example, will sort of separate out into only some of the droplets, and you can see the positives in the rest of the droplets. So you'd get a number. It would just be lower than you would expect.

Some things like EDTA, if you put them in there, they're small enough they're going to basically distribute to all the droplets, and you have inhibition. But there haven't been a lot of really good studies about inhibition. I would say we probably don't know very much. I certainly haven't seen anything of all the drugs on that list. I'd have to plead kind of ignorance about that.

DR. BLUMBERG: Thank you. Oh. I never identified myself. This is Emily Blumberg.

The other question I had goes back to something Randy said before, and I'm wondering about whether or not we can actually make this assumption and whether the FDA has had this experience, which is you said that if we changed the downclassified, that the presumption is the cost would be less. Now, the cost to the manufacturers would be less, but in those cases, does the FDA have experience that the cost of the test to the actual

patient and center is less? Or is that not necessarily a given? I would assume not a given.

DR. GITTERMAN: Two things. One is I certainly don't have experience, and I'm not sure any experience would be generalizable. You know, if one were to say something becomes a generic, it becomes cheaper, and that's before somebody buys up Daraprim or EpiPen. So any generalization, certainly there's a lower -- and I don't like this word -- barrier to manufacturers in many ways, even from the fees at every step. But whether that actually results in a cheaper test for patients, that's, you know, a completely different -- that's something that we couldn't comment on.

I can comment on interference, though. And I think that's really -- of course, that's one of the great aspects of FDA clearance or approval of any devices. We have an extensive -- we very carefully choose the substance, both on frequency, like, you know, this would be disastrous if it actually did have an effect, or on, you know, on probability. You know, certain tests are more like to have certain interference.

It also is true, which would not be true here, if you have large enough clinical studies, then in fact, you could say performance will suffer against the reference method if there is -- or a comparative method, if there really is a lot of intervention.

But it's quite -- you know, there's a lot of expertise, I think, that goes into doing, and I would like to believe that the assays we approve or clear actually have been thoroughly tested for interference, cross-reactivity, reactivity, etc. So that's well done.

DR. HAYDEN: It's Randy Hayden again.

Just to clarify, although what I said was conjecture, I think I was more thinking in terms of cost, sort of more options. And in my experience, as more options are on the market, you tend to have right-sized instruments that you can run more cost effectively in your laboratory, but not direct cost pass-on to consumer, of reduced manufacturer outlays, necessarily.

And again, it's still conjecture, but that's what I tend to have seen is, you know, as there are more platforms on the market, usually I might find one that actually fits in my lab better, and I can run, you know, more effectively for my patients.

DR. GITTERMAN: And that's also a fair question, because again, these are often run on platforms. And not every lab has every platform. So it may make some availability to certain platforms. I suspect Hologics was here for a reason. I say that with a -- for the record, I say that with a great smile on my face. But people have platforms. Of course, it's a different cost to extend the platform.

But if a company -- you know, again, when labs are deciding what to invest in, selection of options may make a difference. Common sense.

MR. SIMON: Tom Simon.

I think I read in the material that there are other findings when they find CMV. Has there been any study? Does a CMV assay, does that also bring out additional infections? Has there been a study? I'm sure there has. The relationship of CMV and other infections, and can that extrapolate to -- they know if they don't know?

DR. GITTERMAN: I could answer this --

DR. PETTI: I'll bring --

DR. GITTERMAN: -- but everybody else around the table could, better.

DR. PETTI: Anyone around the table, but I'll bring Dr. Limaye back to the podium. Our expert.

DR. LIMAYE: Maybe just clarifying the specific issue would help me to formulate a response.

MR. SIMON: It would help me too. I'd say -- make sure I say this right. If you do the CMV viral load assay, and there are other findings, as I understand, from the material I read, has there been a study that correlates if there is CMV, or if there is not CMV, and the other

findings of infections, is there a relationship so that you could know, might know if CMV exists, looking at the variability? Does that make sense?

DR. LIMAYE: Would anyone else care to just reframe it and --

DR. PETTI: It's a question asking if -- are there other conditions associated with CMV disease, and if there's an absence of CMV, do we then not consider patients at risk for other diseases?

MR. SIMON: That, but also to determine if there is CMV because of the variability at -- are there relationships between CMV and one infection or another infection or another infection?

DR. LIMAYE: Well, as I pointed out, I mean, there's a number of biological, non-assay-related limitations to using viral load in blood as a predictor of whether this patient's symptoms are really due to CMV or not. And specific examples that I discussed were specific clinical entities. For example, if I -- or I have a twin brother, let's give it to him, he has gastrointestinal CMV infection. His blood viral load might be negative, so in other words, even a good test that sensitively detects CMV DNA in blood might truly be negative, not because of any assay issues but related to biological issues, that there might, in fact, still be local disease within the gastrointestinal tract that's simply not reflected because it's a biologic issue of local reactivation, compartmental infection, rather than one related to inability to detect accurately CMV in blood.

So I mean there are various biological reasons why, despite the best available technologies, that that's just not going to be fixed, rectified in any way by having an accurate, sensitive, specific assay for CMV.

And I think the other issues that were discussed in terms of limitations, one of the most common clinical illnesses that we see and recognize in organ transplantation is the so-called CMV syndrome. We all know it when we see it. But expert guidelines now

recognize the fact that multiple other closely related viruses can cause an indistinguishable clinical illness, and we might with a very sensitive assay say, oh, I think you have CMV syndrome because we detected low amounts of CMV. They had a clinical illness that we would say fits with CMV syndrome, but in fact, in reality, that patient's clinical illness was due to HHV 6, HHV 7, a combination of HHV 6 or HHV 7.

So I think there's just a multitude of limitations, biologic, as well as the ones Dr. Cook described in detail, assay-wise, that can, you know, make it difficult to interpret assays, results.

MR. SIMON: I think I understand that. So what you're saying is, if I understand, if you definitely can tell you have CMV, there are not other infections that will go along with CMV, be present also?

DR. LIMAYE: Well, there are, and in fact, HHV 6 and HHV 7 are concrete examples that tend to reactivate, co-reactivate with CMV in about 10 to 20% of patients, and it just becomes difficult, really, to be able to tease apart whether a given clinical illness is necessarily due to the CMV that we're detecting, its interaction with another herpesvirus, or some other virus.

MR. SIMON: Okay.

DR. PETTI: Dr. Beavis.

DR. BEAVIS: Just -- oh, Kathleen Beavis. Sorry. I am on, I think. This is Kathleen Beavis.

And, Mr. Simon, I wonder if we're sort of circling around this concept that, you know, or this idea that these test results don't stand alone. You know, they're interpreted in the context of, you know, the previous and the subsequent test results, whether they were done with the same method or not. But I'll be honest, more importantly than that, I think they're interpreted within the clinical context.

And I didn't know if that's really what your question was getting at. And obviously, the clinicians at the table are a lot better suited to talk about this broader context than I am, but I think that's where you were headed.

MR. SIMON: I think you put it in better terms than I. Thank you.

DR. GREEN: I want to add -- Mike Green.

I want to add an additional clarification, which I think is sort of relevant. We don't actually know for certain that having a positive and quantifiable but low test is an actual indication to keep treating. Our standard of care has been to do that, based on a study or two, but we don't actually know for sure if that information alone really indicates -- and the reason we do that is risk of recurrence. I mean, that's sort of the reason that it's done, that if you stop early, the clinical disease may recur, and there could be a risk of resistance with that.

In fact, work that people are doing at this time is trying to take other information together that is measuring the body's immune response present in combination with the presence of the CMV detectable load, to maybe get a sense of whether or not you need to keep treating or even initiate treatment. I will tell you that that is still, that measurement of the immune response is still sort of at an experimental level.

And so it's something that, when we've had consensus conference discussions, actually at the last consensus conference, it was included in the document that came out, but there was a lot of debate of whether the data were really good enough to include it at this time. And there'll be a third version of CMV consensus guidelines come out, by the Transplant Society that Camille is organizing, later on sometime in early 2017 or the spring of 2017.

So this is part of our dilemma is we don't have rocket science knowledge as to if you have a value of X on any assay, whether it's a laboratory-developed test or whether it's a

FDA-approved with a Class III approval, is if you have X, that you definitely need to be treated. And, in fact, if you recall, what there's an indication is, is that if you are being treated, and you're being followed over time on therapy, the approval is for that this is a useful test because if you're not having a fall on your load over time on therapy, it has a clinical implication that there's a problem.

And so I think that that's really some of the other issues to take this into the context of the level of requirement we're putting on these assays.

DR. BADEN: Lindsey Baden.

I look at it -- I think we have to separate two issues, in my mind. One issue is what can we detect? Do we detect it reliably and know that if we say it's 6 inches, we know it's 6 inches? Is CMV present? Is it present at a certain quantity? I think, to me, that's a key question as to will the diagnostic test give us information that we know what it means, that we know what we're measuring, that is separate from what do we do with the information?

And I think that is a very complex discussion as to once you know it's there, what do you actually do clinically? And I don't think that they are the same question. I think they're very different questions.

DR. ISON: Mike Ison.

Just a quick point. FDA doesn't have purview over clinical decisions, correct?

DR. GITTERMAN: No. And I would go so far to say that I would assert the vast majority of clinicians don't know if the test they ordered is Class II or Class III or Class I, that I think Dr. Baden has phrased it absolutely correct. But there is a lot of discussion about clinical decision software. That's a different realm. But no, we're not regulating you, in particular, as yet.

DR. PETTI: Any other questions?

DR. SCHAENMAN: This is Joanna Schaenman from UCLA.

I wanted to make one final point about Mr. Simon's question. I think the multiple answers you're getting, and I think the enthusiasm with which we're answering your question, shows me that you really put your finger on a very essential question and conundrum in the field of CMV.

I read another aspect of your question, which is what is the negative impact on the patient if there is a false negative CMV test? I think that was part of your question as well. And I want to go back -- we're all talking about CMV biology, to a point that was raised by Dr. La Hoz, which is that we typically do serial CMV testing. So certainly the best possible scenario is that the test is 100% sensitive if there is even one copy of virus we know. But I think the reality is that if there is CMV reactivation and amplification going on in the patient, and serial testing is performed, eventually it should reach the threshold of detectability.

So a single false negative test, for the level of CMV, would be mitigated by the fact that in clinical typical situation, repeat testing would be performed if the patient is still at risk, and therefore that positivity would eventually come out, again.

MR. SIMON: Tom Simon.

And then the reclassifying to Class II, that would help, would it not?

DR. COOK: I mean --

MR. SIMON: Would that -- I mean --

DR. COOK: Yeah. I mean, it's hard to say, but I guess that -- but going back to what Dr. Kotton said, that we also struggle, at UCLA, with patients who live far away. Maybe we'd want to test them within a week, within 3 days, but there's logistical difficulty. So anything that would increase patient access, I think, might also increase safety.

DR. ISON: So Mike Ison, Northwestern.

So I'm going to be kind of a naysayer for some of this. I think -- I agree with you, and

I think everyone's said a lot of the same thing, that, you know, there's some challenges with access, and it's oftentimes when people are far away, the timeliness of the results and the variability of the results that we have.

But again, the move to a Class III -- or Class II classification for these assays may make it a little bit easier for newer assays to come to the market. They won't solve the problems that we have with the currently approved assays, since everything will be compared to those assays, unless I'm wrong.

(Off microphone remarks.)

DR. ISON: And I -- so again, I think that these -- from my perspective, I think that we've been focusing a lot on the problems with the available assays. And this reclassification will not address those problems. I think that having -- if we had a hundred assays on the market, someone in rural Wyoming is not going to have improvement in access to CMV testing. Nor will they -- again, I would say, with relative confidence, but I can't say for certain, that the turnaround time would also probably not significantly improve.

The cost may be a little different. There may be more options, so that instead of going to one lab, they may have a choice of two. So we could go 5 days instead of 3 days, something along those lines.

But I think, as we think about how we're going to think about this reclassification, I think we have -- I think we've been kind of moving pretty far down solving problems that aren't relative to this reclassification discussion today. And I think that it's very important for us to really focus on what will this reclassification do. What will -- what are the harms? The part that I am still not clear on is what's the down side of going to Class II?

Again, I understand that there is differences in regulations of what new companies will have to do, but they will be having to compare to an assay that, I guarantee you, all of

us are using. And I think that's where I'm struggling. So what's the down side to the reclassification?

I think a lot of the concerns that we've raised are things that will not be addressed whether it stays Class III, whether it goes to Class II. I think we could come up with some mitigating -- or some special circumstances that we basically can craft to improve on some of this. But again, in the end, they're going to be compared to already approved assays, which we already have flaws with.

MR. SIMON: If I can just respond. If it helps one patient, say a patient who's closer to Dr. Kotton, regardless of Montana being involved, it's going to help. And not to mention the cost involved, apparently it's going to be less costly, correct?

DR. ISON: I would say that the actual cost that patients pay will be not significantly different. Over time it will probably go down as there's, you know, improvements in technology. But I think moving from 3 to 2 is not going to have a huge impact on the cost.

And I think that we're not talking about -- every single one of us has access to CMV assays at our transplant center, that we probably have the result the same day. The challenge and the access is not patients that are coming to the transplant center. It's the patient that lives 3 hours from Chicago or 3 hours from Boston, or in Wyoming, where they have to go to a centralized lab, oftentimes have it shipped somewhere else.

And again, I think that's where we need to be thinking about, that having 100 tests versus having only these 2 tests that are currently classified as Class III, and having the option of newer tests that have a lower regulatory hurdle I'm not sure will affect that.

MR. BRACCO: Dan Bracco. I guess the question that we all have to ask ourselves is can we afford more variability in the science. Because the more tests you have on the market, obviously the more variability you're going to have. And as I said earlier, when you compare to another device, and then this device compares to this device, so all the experts

in the room need to think about that. And it's just inevitable. Lower barrier to entry, more tests on the market, more variability. And can this science afford that?

DR. BEAVIS: Yeah, this is Kathleen Beavis.

And I'll be honest. That's one of my concerns as well and something that we have to consider this afternoon, if we do think we can put special conditions on. And I'll be honest; I'm going back to the history with HIV testing, when -- you know, and right now, you can go do the different tests and essentially get the same result regardless of what manufacturer you go to. But that wasn't the case 15 years ago, when if your patient was being followed by one manufacturer's assay, you had to pretty much stay with that assay.

And, you know, that's just something to consider for this afternoon. You know, with lower barriers to entry, the patient who lives 2 hours from Chicago might not want to drive up to, you know, Northwestern or might not want to drive to Hyde Park. They might want to locally go to a laboratory that performs a different method. And I think that's one of the challenges that we have.

Even if we say that these methods have to be comparable, we still have problems at this point with comparability between different methods, different laboratories doing this test. And I'm just concerned about the serial tracking of patients.

DR. BADEN: Dr. Beavis, how did the HIV community standardize their assays so they're comparable?

DR. BEAVIS: So I will -- my perception on that, the testing just got better and better and better. And, you know, I remember initially HIV testing, lower limits of detection were 75. They were 50, 19, 12. And I looked at -- you know, I've been on the CAP Microbiology Research Committee, where we look at the different manufacturers. And manufacturers have been broken out by peer groups. And we had to do it that way because if you were using -- even among the different Roche technologies, if you were using cobas or TaqMan,

you were in a different peer group, and your results worked that way.

But as testing got better and better, the results were more --

(Off microphone comment.)

DR. BEAVIS: The results were more comparable. But that took a lot of time.

DR. PETTI: Yes. Dr. Green.

DR. GREEN: So I think just -- I think one last sort of clarification for the advantage from going from III to II is the barrier for CMV really comes down to perhaps a little bit of increased variability, if you're in the remote areas, but also the potential advantages of not using laboratory-developed tests, where every one of us at this table are using likely an internal test. And for whatever reason, although there are two commercially FDA-approved tests, most of our institutions have chosen to not use those and have implemented their own.

I don't know whether that's true of all places or not. Maybe not at Mass General, because they just went from pp65 to implementing something. But, I mean, I think that if we were to raise our hands on a Panel here -- I mean, I'll happily tell you that Pittsburgh uses a laboratory-developed test. And up until 3 years ago, the Children's Hospital Pittsburgh used one, and Presbyterian Hospital, which was next door to it 7 years ago, used another.

And so I think the potential advantage to moving in that direction, whether that's mandated or not by a guidance that may or not eventually become the rule, the logic behind it of whether there's -- that you are using tests that have had some regulatory clearance, and if there's an advantage to it, then lowering the burden that you -- to have the industry bring us product is, I think, what we accomplish by going from III to II.

DR. PETTI: Dr. Kotton.

DR. KOTTON: Camille Kotton.

I would just say that I don't -- it's not my perception that the majority of transplant programs are doing LDTs for CMV at this point. That's what I've seen in surveys.

MR. BRACCO: This is Dan Bracco.

I just want to comment that I haven't heard anything, any studies or anything that comments on downclassifying a medical device and whether or not lab-developed tests diminish because of that. I'm not aware of anything in the literature that supports that.

DR. GITTERMAN: Steve Gitterman.

I generally think lab-developed tests should be considered out of scope. I mean, really, what we're considering right now are the medical issues. Can the risks be mitigated, and can we have safe controls that do that?

I appreciate the discussion's gone around, and certainly we don't mean to stifle any type of discussion, but it really shouldn't be an issue, and solely be promoting public health.

DR. ISON: So I have -- and this is more directed at the lab people. I totally agree with you, I think, with the HIV paradigm, where we've improved. I guess the question that I have is could we craft controls so that basically people are moving in that direction, because the one thing that I will say, too, is that even for the same assay, there's still a little bit of variability between labs. And so, you know, so even if, you know, there was only one test all of a sudden available and everyone started using it, there would still be some degree of variability.

So do you think that this is something that we can craft something? Or do you truly feel that having the overall approach requires the level of control that a Class III would --

(Off microphone comments.)

DR. GITTERMAN: FDA-recommended comparator.

DR. BEAVIS: Dr. Ison. Yeah. You're putting to people -- I'll be honest, I'm going to -- this is Kathleen Beavis.

I'm going to defer to my colleague, Dr. Hayden, who's had a lot of experience with the WHO and this.

DR. HAYDEN: Well, and -- this is Randy Hayden.

And Linda can obviously comment as well. I mean, I think we're not going to solve this through special controls. We're not going to make the test equivalent in precision to HIV. You know, I think the problems have not all been solved. So what we can do is try to ensure the manufacturers, you know, do all the -- is currently -- or make use of all the information that is currently available, to make the tests as good as they can be and to harmonize them as much as they can.

But it still won't solve the problem per se. I think that still is going to require further evolution of the field, in my opinion.

DR. PETTI: Great discussion. Yes?

(Off microphone comments.)

DR. COOK: I swear.

DR. PETTI: Well, apparently, I'm the only one with the power.

DR. COOK: Okay, then, am I invited?

DR. PETTI: But please, Dr. Cook, please. Yes.

DR. COOK: I would just add that I don't think that all these studies are in CMV, but I think there's pretty clear data that if we use an international standard to standardize a bunch of LDTs, that they're better afterwards than they are before, for the most part. Maybe not in every test, every exception.

And I also think that there is probably good data out there for people who compare an LDT performance to an instrument or a manufacturer who makes a particular assay across multiple laboratories. So there's actually a couple of good studies from Europe that have been published, one in particular in France, and I'm not even sure if it's CMV. But

essentially, if you use the same instrumentation across labs, it's better than the same LTD across labs. So I think both of those steps are steps forward. They're not going to fix everything, as Randy said, but I think both of those steps independently can overall improve the results.

DR. PETTI: Thank you, Dr. Cook. We will adjourn for lunch right now. And I advise everyone not to discuss the meeting topic during the break amongst yourselves or with any member of the audience. And we'll resume at 1 p.m. Thank you.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

DR. PETTI: Hi, everyone. At this time, we are now going to focus our discussion on the FDA questions presented by Dr. Gitterman. Copies of the questions are in your Panel folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the Panel packs, the presentations, and the expertise around the table.

With this said, I ask each Panel member to identify him or herself each time he or she speaks to facilitate transcription.

We will first show the question. There's only one.

(Off microphone remarks.)

DR. GITTERMAN: Book. And it's an essay question, so you'll be graded appropriately on a curve.

But do Committee members believe that special controls, in addition to general controls, which is the definition of Class I, are necessary and sufficient to mitigate the risks to health presented by quantitative CMV viral load assays?

In addressing this question, please discuss the proposed special controls that Dr. Whitaker had brought up this morning and are still in your packets, and any additional special controls -- please, and I can't emphasize that more strongly -- that would be recommended if reclassification is considered for CMV viral load assays.

As a part of the question, and part of your discussion, regarding reference standards, and obviously, the discussion this morning was almost a preamble, as a follow-up in the discussion, if you feel you'd want to comment, please talk about the commutability of FDA assays calibrated to standard reference material.

And, Dr. Chou, of course, look forward to your comments.

The challenges of commutability at concentrations near the limit of quantitation -- you can get a very, very high R-squared but have different sensitivities right at the LOQ -- and what the implications that are for both treatment and preemptive therapy, the benefit of other alternatives, BAC or whole virus standard reference material, and the effect of the sample matrix.

And are there any questions about that? Is there anything about that that's not perfectly clear? I hopefully will not be much in the discussion, but if there's any clarifications necessary, please -- and of course, we have quite a FDA representation to add clarity.

Thank you, Dr. Petti.

DR. PETTI: Would anyone like to start the discussion?

Dr. Baden.

DR. BADEN: So am I voting? Or am I just giving my thoughts.

DR. PETTI: We're deliberating.

DR. BADEN: Deliberating?

DR. PETTI: Yes. Your thoughts on the first part of the question, and then if you feel that you can do that, then even proceed to the second part.

DR. BADEN: I mean, I think that, in reflection, I think that -- and Tom sort of was drilling at it earlier, about what are we trying to accomplish here? And Michael -- Dr. Ison also got at the issue of trying to narrow our scope.

I see two key issues. One issue is what we think about the qualities of the test to give a result that is reliable. And Dr. Gitterman already got at issues that are implicit in that related to matrix. We heard things about target. There are a variety of analytic that are largely physical properties of the device, and then really understanding the matrix. And, you know, Dr. Blumberg's comments, I think that EDTA is different than heparin, which is

also different if there's renal failure or liver failure or con-meds or other kinds of issues. So then -- but to me, that is a process issue about sorting out how to develop a test that is reliable and interpretable.

And then I think the second issue is what do you do with the information when it becomes available? And that, I think, are two separate issues. And then how do we sort of think that through in a paternalistic way versus here are the information? And then we have to understand that the community is thoughtful and can use the information thoughtfully, so that we make it easier to generate the information.

And I think the HIV example is a challenge in that they didn't start where they are now. And how do we sort of help push the field to get where we think it needs to be and to align the incentives and the forces to get there? And I think there are different ways to deal with -- to mitigate the risks by those different issues, and there are different ways to sort out how to incentivize the community so that we can get more testing available but guide it in a way that can elevate the quality of the information.

And I think both are achievable. And then it's a matter of giving the FDA sort of guidance as to how to think about that. But I think we have to think about the question as to what question we're answering. That's thoughts rather than votes.

DR. PETTI: Yes.

DR. CHOU: Yeah, Sunwen Chou.

So I think, as far as the main question, my answer would be yes, special controls, in addition to general controls, are necessary and sufficient and should be specified in, I suppose, enough detail to give potential new developers guidance on what those controls should be.

I think, for the moment, as far as the standard calibrating control, the WHO standard may be what we'll have to live with because people are already starting to calibrate some of

their, you know, own assays against that standard. We know that that standard has shortfalls, such as it not being able to represent the diversity of strains that's out there, the physical form of the DNA in that control is probably not a good reflection of the size composition of the DNA in plasma.

And so the way to word that would probably be that, you know, that it needs a calibrating control that the FDA recognizes as being state of the art. And then that in addition to that calibrating control, there would also be the need to show that any newly developed test should be tested against a proficiency panel sample of real world specimens that have been tested against, you know, currently approved methods, at least as a means of comparison, that the performance is, you know, similar.

DR. BADEN: I wasn't quite ready for your question to me. I mean, I would say there are two things that I would push for, the standard. And perhaps instead of a gazillion dollars to do premarketing studies, one could imagine pushing the industry to share in the cost of developing a high-quality standard that could allow tests to be interpreted across testing platforms.

And then the other issue is interpretability. And I do think that, you know, I'm not -- I think we need to put out there that there is an expertise to interpreting a test result, rather than the test result stands in absolute to guide the decision making. And there needs to be a stronger investment and a stronger push that, you know, what to do at the lower limit of detection.

I am not sure that that is an issue about making the test more reliable, because you may have variability at the lower limit of detection, and it comes to what do you do with the information, rather than do you believe the information is a number. And that, I think, then gets to the issue of, do we really empower the community, the field, to say that the data generated actually have another step to figure out how to use it.

DR. GITTERMAN: Just to clarify that for the discussion, I would differentiate LOQ from variability. Tests may have different sensitivities such that one assay -- and I could -- I don't want to cite specific samples, but I could send you abstracts where it may be almost uniformly negative from let's say 0 to 200, where another assay may show detectable virus in that range. That's not quite variability. That's sensitivity.

DR. BADEN: But I accept that at the lower limit of detection. Some assays may be twofold, fourfold more sensitive. And there'll be some variability of the analytic technique. So you have both. I accept that. You still get a number that is at the very low end. What to do with that number, because the implication is you get a test result. The troponin is 2. Ergo, you must do something because that tells you a diagnosis.

I am not certain that a CMV viral load, detectable right at the lower limit of detection of a reasonable assay, equals you must treat. I think, you must first believe that that number is real. Then the question is what do you with that number? And I think that's part of the challenge in this is we're looking at a test that is universally interpretable by everyone equally, where the test is very context-dependent to interpret.

DR. GITTERMAN: So just one point to the Chair. If the group could just confirm what Dr. Baden is saying, is that for somebody who's treated, if they had an -- never mind.

DR. ISON: Yeah. So I was going to totally agree with Dr. Baden.

This is Mike Ison, from Northwestern.

So -- no, no. No. But, I mean, I think that the reality is just a few years ago, the general limit of detection was somewhere between 5- and 600 copies. And so many of the patients that we are getting anxiety about, because their viral load is now 138, we would have not known and not treated just a few years ago.

And it wasn't as though people were dropping like flies from CMV in that setting. And I think one area of weakness in data is that we switched from assays that had a very

different lower limit of quantification to one that has a much lower limit of quantification and are being driven to do things, because we see a number that we would have seen as negative before.

(Off microphone comments.)

DR. GITTERMAN: This is Steve Gitterman.

The question is let's say someone is being treated because they were positive, and now you're looking to stop treatment when they're, quote, "non-detectable," or that's going to determine --

DR. BADEN: It's the same problem. I don't accept that the number equals the treatment. And, you know, and that's where I would say, in the label and in our thinking, I think we have to add a new category, which is the data generated that we consider reliable and valid, require an interpretation. Because in a cord who is right after transplant, I may treat, while someone who is a year after transplant, I may not because they have to reactivate a little bit to generate endogenous immunity.

So that's where the context really matters. And I think the challenge with diagnostic tests is you're saying here are the test characteristics. And you are also foraying into the use. And the use, I would argue, requires expert guidance. And I would strongly advocate, in the label and in our practice, we figure out how to say that this should be used by people skilled in the art and that these tests are not absolute in isolation.

DR. ISON: I think the other --

Mike Ison from Northwestern.

I think the other thing, which is sort of what you're getting at, is not so much the preemptive approach but the treatment approach. Again, I'm going to go back to what I said. Three years ago, that 138 was a negative, and we would stop. And the reality is there isn't -- there have been some studies, but very few, that have looked to say, well, what

happens if you get to 200, which would have been negative a few years ago, and decide to stop treating then versus 130, versus 600.

I mean, we have a paradigm at our center that we basically have an equivalent to what was 600, and that's what we use. And we've been having a very similar rate of relapse, rate of failure using that. So again, I think that the absolute number may not be the correct answer. It may be how the clinician utilizes it.

DR. LA HOZ: Ricardo La Hoz, UT Southwestern.

So do I believe that special controls, in addition to general controls, are necessary and sufficient to mitigate the risk to health -- well, you can read the rest. And I think the risks are false positives, false negatives, the variability. And we also need to think about the benefits. Somebody spoke about the better access for tests, for patients, you know, quicker turnaround time in the test results. And I think that the risks of false positives, false negatives can be mitigated mainly by who interprets the test and putting a comment there, but also by sequential testing, which is what many of us do.

There might be a low-level PCR, and we assess the net state of immunosuppression. I don't think this is going to replicate that fast. Maybe I need to check another one in 3 days, 2 days, I don't know. So I think those risks can be mitigated by both who interprets the test -- that goes back to what we need -- we may have to put on the label, and two, by sequential testing.

And I think that the benefits of more turnaround time or quicker turning around time and better access to care, in my mind, so I think that we could mitigate those risks, and the benefits will be high.

MR. BRACCO: I just want to make sure we're all clear on the questions as well.

And, Dr. Gitterman, if you could opine on this.

I think the first question we need to ask ourselves is, is the group comfortable that

we downclassify this test from Class III to Class II?

And then the second question, I think, has to be if we believe that, then what type of controls would we put in place to mitigate any potential risks that arise from that downclassification?

So when I hear the comments, it's almost like it's a done deal. It's already downclassified. And I just want to make sure that we're all comfortable from that aspect.

And, Dr. Gitterman, I'd appreciate --

DR. GITTERMAN: No. You've phrased it exactly right. I think from the comments that have occurred so far -- and we certainly want to hear from everybody -- but that's the inference. One, do you think this can be down -- reclassified, downclassified such that it maintains its safety and efficacy and mitigates the risk? And if so, based on what Dr. Whitaker had showed earlier and all the extensive experience around the table, are there other things we, you know, we should be putting in the special controls to make sure it maintains its safety and efficacy at that, at the next level? Or at a Class II level, excuse me.

DR. GREEN: So this is Mike Green.

I'm going to just -- since we've broken it into two questions, I'm going to answer the first question only at this time.

So from my perspective, I believe that we can safely reclassify from III to II for CMV quantitative assays serving the roles that we've talked about it doing. That is going to be blood, but maybe we talked about serum or plasma, for both monitoring patients on therapy, but also for sort of surveilling patients to inform preemptive therapy and/or to make a diagnosis of CMV.

And sort of my sense for that is that, you know, I use -- I've already said this. My institution uses a laboratory-developed test. And I've been using that test for 10 years, and

I'm comfortable that I'm able to achieve the goals that we're talking about these doing. And so we'd be putting a higher level of control in place.

I think we still have to address what the special controls would need to be. But I think we can design those and that we can safely reclassify from III to II. That's my opinion.

DR. BEAVIS: Kathleen Beavis.

Again, just -- ditto. I think we can do it, and I think that we need to focus on what these controls can and should be.

DR. MEYER: Dan Meyer, Dallas.

I agree with the other sentiments, that it can be classified, downclassified. And I do agree with like what Ricardo said, about, you know, one is ensuring that the interpretation is performed by a trained probably transplant professional, and as well, the serial, sequential determinations of the CMV to follow that.

And I think -- well, then I'll have some comments afterwards regarding the special considerations.

DR. PETTI: And as we infer, but we never heard affirmative, but we'll just do Dr. Baden, Dr. Chou, and Dr. La Hoz.

DR. BADEN: Yes. I didn't -- so I think that it can be downclassified from III to II. And then the question will be how to fill in what those special conditions are.

DR. CHOU: Sunwen Chou, agree.

DR. ISON: So I completely agree. Again, I think if you use the flow diagram that we were provided as part of our education earlier in the day, the first question, which is the question we're being asked is do the Committee members and myself believe that special controls, in addition to general controls, are necessary and sufficient to mitigate the risk. And I think that is a very easy yes. I think we can craft those.

And that being said, then that would shunt us to being very safe in advising that this

move to a Class II agent or device.

DR. BEAVIS: I believe that we've had some very well-informed discussions throughout this morning and this afternoon. And we have identified the clinical risks. And I believe that there are special controls to mitigate these risks.

DR. SCHAENMAN: Joanna Schaenman, UCLA.

I agree with the sentiments that have been expressed previously, and I also like to think, as I think was kind of hinted at by some of Dr. Gitterman's comments earlier, that maybe we can see this as an opportunity for improvement, both within the field of CMV and also to kind of lay the groundwork for what is the kind of information and what are the types of special controls that would be needed for other viral tests.

But certainly, when we look at the Class II and other Class III products, it seems to me that CMV PCR diagnostics have more in common with rapid TB tests than, say, a ventricular assist device or other very high-risk products.

It certainly makes sense historically why this device ended up in Class III. There was a time of great patient death, morbidity and mortality, and lack of knowledge in terms of how to interpret the test. But I think that at this point in time, there's been a wealth of scholarship, including, you know, many wonderful articles by many of the people in the room, that I do agree that we have the tools in hand to craft special controls. And I see this as an opportunity for improvement in the field.

DR. WELCH: David Welch -- excuse me, Dallas.

I agree with the proposal to downclassify to II, and like Dr. Green, I oversee a laboratory that performs a large number of LDTs on a daily basis for various viral load assays. And I must say that there's one thing that really stands out that I think is able to be solved with the special controls, and that is the variability of the calibration standards. And if this can be corrected through the manufacturing information special control, I think that

will go a long way to mitigate the risks.

There are a couple of secondary issues, the intervariability -- interlab variability, which I think can be addressed as well through special control mechanisms and the commutability of assays. So I fully support the change from III to a II.

DR. PEREIRA: Marcus Pereira from Columbia University.

I also agree with the downclassification to II. I think, like we're all alluding to, the details will matter a lot in terms of this, these special controls. And I do believe that we can probably craft fairly sensible, good, and hopefully long-lasting special controls. But as how many have alluded to, the field is evolving, CMV is evolving, the labs will evolve, and patient care will evolve.

So my hope is, as we create these special controls, that there will be also an opportunity to revise them in a few years and see how well they are doing. Perhaps there will be certain things that we get right, certain things we get wrong, and have some instrument to evaluate the effect of these special controls, particularly when it comes to the standardization, which I have the feeling will change quite a lot in over the years to come. And we should have some way of keeping this updated.

DR. GITTERMAN: That's a very good point. Usually there's no means to revise the special controls, but there's ways to write them that allow that generalization and include those opportunities, like just -- I made a point to Dr. Ison earlier, when -- to avoid some of the drift, so to speak, in performance, one could say an FDA-chosen comparator, which allows us to recommend to a sponsor, instead of using the worst possible assay, which hopefully would not happen, that we can recommend a specific assay or as deems development.

So we wouldn't -- we are likely not to have the opportunity to change the special controls, and, you know, we've had a -- obviously, done this, had some experience with this.

If we write them correctly, like in the expression Dr. Welch said, had mentioned earlier, we could ask for larger reproducibility studies that we would normally do to ensure across laboratories. So there's ways to do it, so it's a very good point. And, you know, I appreciate you bringing it up.

So we'll have to pay more -- in context, so we'll have to pay more attention to how we craft them.

DR. PEREIRA: Sure, and --

DR. GITTERMAN: Thank you.

DR. PEREIRA: -- one additional point is we've been talking a lot about the interpretation of the results, and perhaps putting some language in the device labeling on sort of preference for experts to interpret these results. I think we'll all admit -- I mean, many of you have read the device labeling, but probably many will not. So I wonder if really that's the right place to put sort of clinical guidance or at least some form of expectation.

And I like that the language sort of had here recommendations to follow published guidelines. Perhaps that's the better instrument to sort of have the language in terms of how to interpret these results. And perhaps even we should urge guidelines in the future to perhaps also state what would be the preferred standard for future assays. And maybe that would be another instrument.

DR. HAYDEN: Hi. Randy Hayden, St. Jude Children's Research Hospital.

I pretty much agree with what everyone has said in terms of believing that special controls, in addition to general controls, would be necessary and sufficient to mitigate risks and that classifying this as a Class II assay would be appropriate in this case. I think a lot of the points are, you know, well taken. I think that serial sampling is certainly a way to mitigate risks. And that's particularly so, I think, you know, and one could draw parameters around the amount, a degree of precision, and interassay agreement that would be needed

to get to a point where you didn't need to do that.

But I think, as the field stands now, doing serial assays would be probably -- and preferably with the same assay, with the caveat that you may want to re-baseline patients when they move to different assays, might be an important way to mitigate risk associated with interassay variability.

But, in general, you know, again, we can hash out some of the controls, and --

DR. BLUMBERG: Emily Blumberg.

I agree with everybody up to now, and I just want to point out that I think, in Kathleen Whitaker's presentation, she actually outlined some, a really good start for what the special controls might be, and chief among those being analytic studies, which I think are really important in making sure that the analytical studies require comparison to an FDA-approved standard.

So I think actually there's a lot of groundwork that's already being done for us. And maybe when we get to talking about what the special controls are, it might even be worth revisiting her list, which hits a lot of topics, I think.

DR. KOTTON: Camille Kotton. I'm also in favor of the downgrade from the III to the II. And I do think that this will hopefully help mitigate some of the overall risks of not having all the diagnostics, big picture, longer term, maybe not having all the diagnostics that we need, because we really do need additional diagnostics to help save patients' lives.

And I concur with Emily, that this list of special controls is excellent. And I think that that's where we can really help. I don't think the FDA is in the position of dictating what physicians do, or clinicians or laboratorians, as far as clinical care, so I'd be a little more cautious about that. But I do think that there's a lot of good things listed here.

MR. SIMON: Tom Simon. Pardon me.

I agree with the reclassification from III to II. From a patient standpoint, there's

always going to be risk. You look at the safety and effectiveness, but there's always going to be risk. The patients need the CMV viral load assay, and they have to have accessibility to it. So my thought is, is that if this Panel, made up of doctors, physicians, who have the experience and the know-how to put together sufficient and appropriate special controls, if you can't do it, then nobody can. So I think it's in good hands, and I recommend it.

DR. FLATAU: Arthur Flatau.

I agree that we should reclassify this as a Class II device. I think one thing that hasn't been mentioned this afternoon that Dr. Gitterman mentioned this morning about, you know, if we have these devices are predicate devices, then we are showing new devices are equivalent, that we may sort of drift to being less reliable. But I think the benefits of having more tests, perhaps having more tests available for patients who are not at their transplant center probably outweighs that.

I know, in my case, I had my transplant in Dallas, and I live in Austin, and it's about 200 miles away. And traveling back to the transplant center, I didn't -- they didn't -- this CMV -- these tests, I'm sure, did not exist in the early '90s, but for other things, it's, you know, it's expensive, it's a pain. It's hard when you're, you know, just going through a transplant. So I think that makes sense to do this.

And as far as what special controls there should be, I really have no idea.

MR. BRACCO: I just want to comment, as we go on to Phase 2, special controls, that as Dr. Gitterman pointed out, these are going in the regulation. And even though regulations are a lot easier to change than the law, they're not that easy. So I just ask that we consider that when we decide what goes in those special controls because they may be a little difficult to change but not insurmountable.

DR. PETTI: Thank you. Dr. Gitterman, with regard to the first phase of Question 1, the Panel generally believes reclassification from Class III to Class II. And now we will

deliberate on the second phase of the Question 1.

And I request, if Dr. Whitaker could put Slide Number 13 up. It's Potential Class II Special Controls. I think that would be very helpful as we start this discussion.

DR. GITTERMAN: I think it's been done for us.

DR. PETTI: Oh, it -- oh, okay. Great.

DR. GITTERMAN: Did you mean 13 or 14?

DR. PETTI: Thirteen, great. Thank you. Thirteen.

So we've been doing a lot of talking about special controls, and now might be a good time to discuss how we can mitigate these potential concerns that we have.

DR. KOTTON: So we talked about, in the label, including -- and perhaps this is right, and perhaps it's wrong, but to incorporate guidance suggesting that the data should be interpreted by an expert with clinical -- someone with clinical expertise.

And then I personally would consider including in the label the importance of why the right specimen should be sent and why this should be done on plasma. I guess there might be some conflict there where it's approved for plasma. And so why would you include the fact that whole blood should not be sent, but it would still be helpful to know why we don't recommend other specimen, or why other -- why there's risk if other specimens were sent.

DR. ISON: The only down side with that is then, as we heard earlier, there's a lot of off-label use of these assays for BALs and whatnot, CSF. And so that may inhibit utilization.

DR. KOTTON: It shouldn't inhibit it any more than --

DR. GITTERMAN: Off the table. Off the table. It should address -- and I apologize. It should simply address the approved use where you should not be labeling it for off-label use.

DR. BADEN: Which is plasma. The question of other use may be done clinically, but

it's not approved. And I think any use requires a data set specific to that use. And we can't just extrapolate because it works in one matrix, that it'll work with the same characteristics in another matrix.

DR. KOTTON: You know, I'm sort of secretly hoping that if it's approved for plasma, that's all we get. So we get a bunch of purple-topped tubes. That's all the data we get.

DR. GREEN: But I want to have the clarification from FDA of we're not necessarily imposing that all we think that they can do is do it for plasma. What if they purported to -- came with an application for Class II where they want to do plasma and whole blood, and in their proposal, they said we will use the licensed comparator, which is only licensed for plasma, but they compared their whole blood to the licensed comparator in whole blood?

I don't know if it's our -- if we're only being asked to say that, or not, whether we recommend it only be in plasma. But I don't think that that's necessarily been discussed at this time. Maybe we are discussing it. But I think somebody coming, a sponsor coming with a proposal could try to have it cleared for any of the sites, right?

DR. GITTERMAN: Very quickly. One is we will label it appropriately for what it has been proven to be safe and effective for. And we've gotten your message loud and clear, and we can do that. If a sponsor -- and I would say your inference is correct. It's implicit that if we think it can be Class II -- excuse me, and safely regulated on that basis -- it likely can be so for other matrices. But again, that would require proof for that, and if we were to label it to add that alternate intended use, it would address exactly what Dr. Kotton said before. We would do everything we can to ensure that, for whatever there's been, the sponsor supported, that we can do it for.

But I think there's two separate questions there. One, how should we label it? And I think we've heard that loud and clear. And two, this is not, in any way, shape, or form, closing the door on other matrices, but in fact, the sponsor would have to send a data set in

support through the appropriate studies for that use.

DR. BEAVIS: Right. And a third way, too. So I think we all agree about plasma. And then when we talk about other matrices, you know, one is that the sponsor could bring it through. And then another is at the local laboratory, it becomes a non-FDA cleared or approved test, and each local laboratory director could decide to do it on additional matrices after the appropriate studies have been done.

DR. GREEN: As we discussed before, we're not going to regulate what Dr. Beavis does in her laboratory. But, of course, she's 100% correct. I mean, we all know that this occurs. Let's drop it.

It is okay if you think Dr. Whitaker's nailed it.

DR. GREEN: So are we -- Mike Green.

Are we systematically -- if we use her slide as a guide, are we systematically going through the first bullet, which is device labeling?

And I guess the question is, then, to us, is there anything more that we want on the device and -- on the device label? And I think, so far, we talked about having its results interpreted by someone with expertise. And what was the second?

(Off microphone reply.)

DR. GREEN: Specimen type, which would be whatever, presumably whatever they're seeking clearance for, right? I just want to kind of clarify where we're at.

DR. GITTERMAN: Dr. Welch I believe, or Dr. Pereira, I apologize, one of you two had mentioned guidelines as well.

DR. PEREIRA: That's here, right? Recommendations to follow published guidelines. And that looks pretty good. You want it to be broad, because those would be updated as well, and you don't want to be specific.

DR. BEAVIS: This is Kathleen Beavis.

I would caution us against mandating that in a package insert because I think all of us have been involved in published guidelines. They're typically years behind, you know, the cutting edge of practice, and I don't think any of us want our hands tied with that.

DR. GITTERMAN: Right. In expertise, we could say something like, you know, familiar with current practices. We can craft it.

DR. PETTI: Dr. La Hoz.

DR. LA HOZ: Well, I was going to say expert in use of clinical variables to assess the risk of acquiring the disease and progression to disease, and we can work on the wording, but something about using all the clinical variables available to assess the risk for CMV, or something like that.

DR. FLATAU: Well, as a patient, I guess I hope that all my lab tests are evaluated by someone who has expertise. But it seems to me that the problem is that there's no value -- as has been said before, there's no value that says we should treat or we should -- or whatever. And it needs to be -- the lab test needs to be interpreted with the clinical data. I mean, I think that's the key point that needs to be in the label.

DR. PETTI: I have a question for the Panel. When you receive CMV quant results in your EMR, is it reported as negative or not detected?

DR. BLUMBERG: Not detected.

DR. KOTTON: Not detected.

DR. ISON: So ours is less than the lower limit. It says less than 137 for our assay.

DR. KOTTON: Yeah.

DR. PETTI: Because what I was hearing is, is we were all concerned that the absolute number, we did not want that to trigger necessarily a clinical decision. So is there anything in labeling that you would like to see, as far as result reporting?

DR. KOTTON: Camille Kotton.

It's currently very confusing to people because it'll say detected. And sometimes they think that that's like a qual. But it's actually the quant, but it's so low that it's sort of, you know, below 137 IU or whatever. So it is quite confusing. It would be interesting to think about how to rectify that.

DR. HAYDEN: So --

DR. BEAVIS: So it's -- sorry. At University of Chicago, we do both. We'll say that it's negative if we didn't detect any. We'll say that virus was detected without a quantitative result if it's below our ability to quantitate it. And then between that and the upper limit of quantitation, we actually give a number.

DR. HAYDEN: Yeah, Randy Hayden.

We do something similar, I think. So in the linear range for the assay, which is provided with the result, we give a quantitative value. Above or below, we say detected at greater or less than the limits of linearity. And if not detected, we give not detected.

And just to also say, you know, perhaps labeling would be where we might, if we're not happy with a single result, where we might want to suggest the use of serial samples for interpretation.

DR. SCHAENMAN: This is Joanna Schaenman from UCLA.

I agree that this is an area of concern, but since this is one area where I don't know that we have the answer, I'm not sure we can be definitive in the package guideline in terms of guidance. So hopefully, by getting expert input, that issue can be addressed.

Regarding Dr. La Hoz' question about what exactly should be in there, in terms of other things to contemplate, there was some nice language that was provided to us, I think it was from the FDA. The phraseology was in conjunction with the patient's medical history, clinical signs and symptoms, results from other laboratory tests. I thought that was nice language that would give an interpreter at least a guide as to the kinds of things that an

expert would interpret, but I thought it was also vague enough that it's not committing us, irrevocably, say to some particular standard, especially considering that we're going to have new, hopefully, diagnostic modalities for looking at CMV-specific immune response to be incorporated.

So I think your comment, I think it was Mr. Bracco who said that we really need to be careful with the language, that we're not kind of marrying ourselves to 2016 knowledge but thinking ahead.

The final thing I wanted to say, if we don't want to suggest just look at the guidelines in the packaging, and we're concerned that people don't read the packaging, maybe our take-home message from this is that we, as members of professional societies, need to use those societies and those guidelines as a way of spreading awareness of what's in the package.

In other words, if there's some very nice language that's crafted for special controls, maybe it behooves us within our societies to publicize that information. Maybe we'll never quite get people to unwrap the package insert and read it, but perhaps that information could be made available on various websites, etc., unless that violates an FDA policy, so that we can be sure that people within the community are aware of what the guidelines are.

MR. SIMON: Should there be, for the patient, dos and don'ts, eligibility criteria, history -- I mean, anything like that that should be either in the labeling or package insert or -- package insert. You get my idea.

DR. PETTI: Any of the panelists can respond to that question.

DR. BLUMBERG: Emily Blumberg.

I think we have to be very careful about defining patient populations because our notion of what's an immunosuppressed host is evolving. And it's pretty clear that right now, while we're thinking about this from the transplant lens, especially because so many

of us are transplanters, that there's an ever-growing group of immunosuppressed patients, as we use more and more modalities to wipe out immune systems for a diverse set of conditions, and I think we should not specify a patient population, because I think this will ultimately, potentially have greater use than just the transplant patients.

I also wanted to just bring up, I think, as we're thinking of our special controls, just to re-emphasize the issue, that's it's really important to have analytic studies. And that has to be, I think, front and center to anything, that any test that's going to be brought to approval needs to have adequate analytic studies with appropriate controls, whatever those controls may be. But FDA, I guess the language would be FDA-approved controls. And that's really, I think, probably first and foremost, you know, what we need to say because implementing the test comes after developing the test. And I think test -- so we should be proactive with that.

MR. BRACCO: I just want to comment on the language thing. A lot of folks here don't realize this, but as a manufacturer, we try to have global labeling. It costs us a lot of money to have labeling for the United States and labeling for Asia, if you will. So we like to have general language that we can translate and use on a package insert throughout the world.

So all the criteria for getting the product cleared, that's not a problem. But it becomes a problem for us with the language, if it's too specific for the United States. If that's the case, then we will have to have dual labeling, which costs us money and is a considerable burden. Thanks.

DR. GREEN: So Mike Green.

To Emily Blumberg's point about the analytics, I think, on Slide 9, we've been given a list of about I guess it's 14 or 15 different analytic performance measures that have been mentioned that I think would be worthwhile to sort of hold the development process to.

My sense is that those were similar to what might have been done if it was Class III anyhow. These are precision, accuracy, reactivity, sensitivity, specificity, limits of detection, sample type, matrix, sample preparation, contingence, performance around LLOQ, ULOQ cutoffs -- cutoffs may not be able to be put on this, by the way -- linearity, potential for carryover, cross-hybridization, and stability.

So I think that was a list that was potentially proposed for analytics, and, you know, I don't have the laboratory expertise to say whether those are truly required. And certainly, I think, they're probably feasible if you're willing to put the investment in. But it's a good starting point for us. And maybe our laboratory colleagues can help with this.

DR. BEAVIS: Kathleen Beavis.

I will tell you that as a laboratory director, when I review a new assay, these are -- this is the list that every section director has to bring to me. Did they examine these things or not? And if -- so anyway, yeah. This is very routine for us.

DR. BADEN: So I sort of assumed that these were the general standards, and then there are the special. So what are we adding on that we think is unique to the circumstance?

And there, for the analytics, the issue of multiple target rather than a single target, so you don't have viral escape and loss of detection. I think the issue of clinical performance, because these patients are medically complex, so inhibitors, metabolic derangements, polypharmacy, things that may not be part of the usual development of a test. In healthy people, these tests need to be looked at.

And I think Dr. Blumberg sort of alluded to this, but it's not only the matrix, but then it's the background of the matrix, given the host.

And then to Dr. Hayden's point, there actually, in my view, are true negatives with CMV disease. So I'm not sure -- and that skips to, you know, GI CMV disease, usually in my

experience has a negative peripheral load. And therefore, when I am suspicious of GI CMV disease, I don't use CMV load as exculpatory. I don't use 2 as exculpatory, or 3 or 4. I use clinical judgment to say that the syndrome I'm concerned about does not -- this test does not behave that way for the syndrome, which gets back to the test in isolation could be very misleading.

And that gets to there are true biologic negatives with disease being present, and there are true positives without disease being present. And one has to factor that in, in how this is rolled out.

And then the issue that I think is really important, but is not an easy nut to crack, is the issue of the standard. We have alluded to that before. The Merlin strain is magical but may not be adequate on its own. And I think a fair amount of effort and pushing our industry colleagues to develop a standard, and that that will enable us to understand comparability, commutability, and to really push the issue of a standard so that we can go across assays, across platforms, across centers, and begin to have a way that this may behave like an HIV test.

And that, I think, that if patients move between centers or regions, it would be really nice to be able to use a test that we have some degree of interpretability across days of the week. And it's how to push the issue of the standard development that is actually useful. And I would strongly advocate for that being a special consideration that would be useful, not just for any specific test but for the platform in general.

DR. LA HOZ: A couple questions: Since my expertise is not in laboratory but thinking about the non-inferiority studies, it's always important to think about the margin of non-inferiority, you know, compared to current therapy. So when we decide on the analytics, how are we going to define that margin and therefore all those variables? And I guess that's an open question for the people that have expertise in that.

DR. HAYDEN: Randy Hayden. Just to, again, to comment on the standardization issue, I think that it would obviously behoove the field to encourage further development of better standards. I still think probably funneling that through international groups such as WHO might be a good way to do it. I don't know that necessarily it's a question of finance as much as just pushing the field forward.

And I think that -- you know, so the field is where it is today, and I think what we can do is basically ask currently for manufacturers to define what they're using for standards, how it's traceable to whatever international standard they are using, to define commutability, again, with the state of the art, because that, too, how commutability is defined, is evolving.

But giving that information to the user, I think, is also an important way to mitigate risk, you know, as are other aspects of precision, accuracy, and so forth, the ability to differentiate changes in serial viral loads. And what prediction interval you can expect from a given assay is also important to not always include it.

So again, I think that it is important to continue to push that field forward, but also to be able to work with what we've got now and make sure that there's enough disclosure that users can, again, mitigate risk and use the results optimally.

DR. BEAVIS: This is Kathleen Beavis.

And as a follow-up to your question, Dr. La Hoz, is it fair for us, as this group, to give that charge to the FDA, to come up with a margin for comparability? And I'll give you, you know, my thing. If I'm -- if we want to bring in a new test in the laboratory, we'll often say, oh, you have to get the same exam, you know, the same result as the existing test maybe 95% of the time. For another test, you might say 80% is a good enough threshold. What kind of guidance, Dr. Gitterman, could we help provide for this, or do we not need to?

DR. GITTERMAN: I would suggest -- it's far more -- it's a fairly complex question in

many ways. But I would suggest that, again, and I think this is in the spur of what Dr. Hayden has mentioned earlier, we could use similar thresholds that we've used previously and define that. But it's actually, without wasting everybody's time, a very, very complex question.

If I could just make a point, I completely agree with Dr. Hayden's -- establishing a new standard would be beyond the scope, beyond our regulatory scope. And we couldn't write a special control that says come up with a new standard, nor would that really serve a purpose in a lot of ways.

I completely agree, any efforts -- and if people here feel the current standards aren't good enough to use, that, of course, is very important. But perhaps the most useful way would be to continue the work which we are involved with, and is promoting a more useful WHO or NIST standard.

DR. PETTI: Yes?

DR. ISON: Not related to this. If you --

DR. PETTI: Oh, I do have a question for the Panel, particularly the laboratorians and the clinicians. When it comes to inclusivity and labeling, is there a need to, in the label, say what glycoprotein B genotypes are detected for the CMV assay?

DR. CHOU: I would say no because CMV gB genotypes are really not the same concept as like HCV genotypes. You know, one fundamental difference is that no biological difference has ever been convincingly attributed to specific gB genotypes, either in terms of virulence or response to therapy or how you would handle it clinically.

Furthermore, CMV is such a complex organism that merely typing it according to the, you know, four gB genotypes is really only a small, a snapshot or sample of the genetic diversity that exists. It's a very, very crude, you know, index of diversity.

And I've always been puzzled at, you know, how there are -- some people propose to

use diversity in gB alone as a means of assurance of sufficient diversity in the CMV strains that have been sampled. It could be one index of diversity. So I'm kind of, you know, divided as to whether to put that into regulation, rather than using some more generic definition, like the controls need to show evidence that some reasonable diversity of strains have been picked, or in terms of a calibrating standard, language like an internationally recognized calibration standard, or something like that.

DR. GITTERMAN: Would it be fair to translate this by saying everybody is in agreement with having reactivity or -- what's a synonym for inclusivity studies -- whether across glycoproteins, but there's -- again, if a sponsor does something, we usually allow them to put in the label, but it would not be highlighted as if, you know, that is a goal. It's just saying it includes these strains, as one might do for TB or any other similar labels, or dissimilar labels.

DR. PEREIRA: So just going back to the discussion about providing information for the users, one example, and this might be a general to all your, to all the other academic centers, but for example, *Aspergillus galactomannan*, when we get the result in our EMR, there is a sort of disclaimer at the bottom how one result should not be interpreted, and you need sort of two or three more to get some kind of meaningful clinical interpretation.

Would it be reasonable to do this for CMV, where sort of some of these concerns that the Panel has had, perhaps we could draft a very brief statement on how to interpret a CMV PCR result? Or is it adding too much burden on already overtaxed --

DR. GREEN: I think it's a bad idea to interpret because I'm not sure that we know frequency. There's so many moving parts. I think clinical care has no place in package inserts or FDA regulation.

DR. BLUMBERG: Emily Blumberg.

I think the other thing is, as the assay evolves, you know, interpretations could

change. And if you want language that's going to go across time, or at least longer time, that probably, I think -- clinical interpretation should be left completely out of this. And other than saying, you know --

DR. BADEN: By someone skilled in the art.

DR. BLUMBERG: Yeah.

DR. GITTERMAN: But I thought I did hear the --

DR. PEREIRA: Yeah. Clarifying --

DR. ISON: Well, we said you can do more than one.

DR. GITTERMAN: Exactly. That's --

DR. PEREIRA: But maybe it's just to clarify, not necessarily just clinical guidance but the limitations on the device labeling.

DR. BEAVIS: The limitations, yes.

DR. PEREIRA: You know, sort of there should be -- you know, the same assay perhaps should be encouraged to be used, that should be interpreted by an experienced clinician, sort of vague language that kind of reinforces the lab.

DR. ISON: Not how to interpret a viral load.

DR. GITTERMAN: Right. But I did hear, as Dr. Green had said, that -- again, and perhaps I misheard, that they would like people, like have to -- would like something in the labeling suggested as the clinical circumstances warrant, the test may be repeated if --

DR. GREEN: Yeah. I will -- I'll say it now. Michael Green.

If we -- but I'm sure -- but I thought it was said before is that, you know, that we could have language that clarifies that no single test by itself is necessarily going to be 100% accurate, and repeat testing might be necessary, something that's along that line, that's not an absolute, but puts a little cautionary statement in, because we all do that in our practice anyhow.

DR. BEAVIS: Yeah. We've said, you know, like this test, interpreted in the context of, you know, clinical presentation, signs and symptoms, and other laboratory data. And, you know, I think it's important to have it in there, but I also think we should keep it rather vague rather than prescriptive.

DR. KOTTON: I'm just thinking, I don't really want that guidance that I should do repeat testing. Like my fellow is, you know, somebody's 15 years out from transplant, and somebody randomly sends a CMV viral load, I don't want any kind of information that that needs to be repeated because it shouldn't have been sent in the first place. Like I --

DR. GREEN: Well, I wasn't saying -- sorry to interrupt, Camille.

I wasn't saying that it needs to be.

DR. KOTTON: Sorry. Camille Kotton.

DR. GREEN: It's that one could consider that, you know, because if you're really thinking CMV and you have a negative test, you might want to repeat it so there -- we could ask FDA to try to craft a sentence that says that you could consider using a repeat test if results don't match your clinical expectations, something like that to say --

DR. BEAVIS: This is Kathleen Beavis.

So I'm really going to caution you against advocating for something like that because I, as laboratorian, might think that you should do something. But I don't want to put that in the laboratory record for a variety of reasons. And I hate to say it, but one of my favorite phrases is "as clinically indicated." So it sort of gives you the heads up, without again telling you to do something that if not done could lead to problems down the road. Does that make any sense?

MR. BRACCO: You also have your sensitivity and specificity data in the package insert, so you can interpret that as you will.

DR. BADEN: Would you be okay with, "Any result should be interpreted in the

clinical context by someone skilled in the art"?

DR. BEAVIS: Where would you put that? In the package insert or when the result is reported?

DR. KOTTON: Aren't you saying that for -- Camille Kotton.

Are you saying that for any diagnostic assay? Like cultures, everything.

DR. BADEN: Well, I think it's a generic comment. But for this particular -- because I think both there can be false positives and false negatives, and values you should act on and values you shouldn't act on, that are always context dependent. And I don't think we should be putting in specific phraseology of what you do. Rather, we should point that this is not a yes/no test. This is a test that requires sophisticated interpretation almost every time you order it.

DR. BEAVIS: So this is Kathleen Beavis.

You're proposing, though, that language go in the package insert or when the test gets reported, and in every test result in the EMR? I'd be comfortable with it in a package insert.

DR. BADEN: Yeah. I would go with the package insert, that the result needs to be interpreted, you know, in the appropriate clinical context by someone skilled in the art.

DR. KOTTON: And I believe Dr. Gitterman can chime in, that we do, we have set that precedent in many IBD assays.

DR. BADEN: The problem with the EMR is it's too variable. There is no one EMR.

DR. GITTERMAN: I would suggest the remaining 20 minutes, we perhaps move on to other issues.

DR. PETTI: If we can go back to Slide 13. So we have ample discussion now in device labeling. We have not covered manufacturing information. But we did cover analytic studies, so bullet 2, 3, 5, and 6.

DR. BLUMBERG: I think we did talk about 3, method comparison studies. And Jo said there was a need for comparators to FDA-approved standards, right, to leave it pretty -- right?

DR. ISON: Assays.

DR. KOTTON: Or an FDA-chosen comparator, I think, was the language.

DR. BLUMBERG: Yeah, FDA-chosen comparator, to leave opportunity to grow with the field.

DR. SCHAENMAN: Joanna Schaenman from UCLA.

I just wanted to track back to -- I like the language that Dr. Chou proposed earlier that an international standard should be used, without prescribing which international standard that should be. That would allow room for growth, and the manufacturer would have the opportunity to defend whichever standard they're choosing. But it would just give people the information that we're expecting standardization.

MR. BRACCO: And the standard used should be in the labeling so everybody knows what the basis is for your results.

DR. GREEN: So I think -- I'm going to not try to deal with the manufacturing information. We do clinical performance studies. We sort of talked a little bit as a group that there would be specimens tested in comparison, obviously, to the previously approved Class III and over a wide range of results, as I think, what we began to talk about. But we haven't really resolved whether that would be also sequentially over time and in any particular circumstances.

But, you know, if you had banked specimens, or prospectively acquired specimens that were at the lower end and near the lower limits of detection, some that were negative, some that were positive, at a high level, etc., so that we're looking at comparator performance at the range of results that we would expect to see in our patient populations,

I don't know how to exactly word it, but I think we had some previous conversations about that.

DR. CHOU: I suppose there are various ways you can try and push the diversity envelope. I mean, if you want to go worldwide, you could even say your diversity needs to be geographically, you know, represented around the world or, you know, that you have some genetic evidence that your samples represent true diversity.

You know, I -- again, I think it's probably best to leave those, the regulatory definition a little bit vague, just say adequate evidence of diversity.

MR. BRACCO: We also have to be careful in that FDA is here to protect and promote public health for the United States, and I think it would be unusual to dictate other geographical areas in the labeling.

DR. GITTERMAN: I agree. We actually have in -- I know this wouldn't come with the Committee, but we have actually very well-written guidance on what that has to reflect. We could do this, we very often do this, in terms of the analytical studies. For inclusivity, we may want strains that are many places, because again, strains somewhere else may come to the U.S. But the fact is he's -- Mr. Bracco is absolutely correct. Now, that does not prohibit somebody from having a center or site abroad and using that to support clinical use in the United States, as long as they could show that there is -- you know, would be unlikely to be an appreciable difference.

So, but for us to mandate you go abroad was not, is not within our regulations.

Can I ask two quick questions? One is -- and I hope this would be clear. It may not have been this morning. We have taken it for granted that knowing that CV viral load is taken is clinically effective. We think it -- to be honest, it's impossible to do and not ethical to do clinical effectiveness studies. But we do have questions about the nature of the data that comes in.

Just to perhaps disagree with Dr. Green, it's really not that easy to do a prospective study or even banked samples that contain a diversity or have a lot of samples at certain levels. When we said cutoffs before, we didn't mean specifying cutoffs; we meant levels of which people might take clinical action, 1,000, 2,000, as opposed to just having all samples at 100,000.

But especially as you get fairly low, that's difficult. Where one way we have advocated in the past, with PMA holders, has been that they have a certain number of patients who are followed from the initiation of therapy through the entire course of therapy. Now, that may take weeks, an amount of time, but it tells us, you know, whether there's blips, how responsive it is to therapy.

And that's where we meant longitudinal studies. That's where we meant serial samples for a patient, but again, that's not that simple. In today's climate, there's not that many positive patients. I mean, it requires -- well, that's good, because we want to know that. That's what the sponsors tell us, that, you know, we don't want to make it that burdensome.

But other people have argued -- when I say argued, I meant, you know, they haven't argued -- like yesterday, but they have discussed, you know, could this all be done through contrived specimens or perhaps just through getting enough, you know, cross-sectional samples? And I think, you know, we have a particular view on that, but we'd welcome some input on that on the Panel.

Another question would be, just before going too long, is the question of postmarketing studies, which I think is very important. Certainly, as Dr. Hayden and others talked about, if there's some flexibility in the standard, we also -- it would be perhaps -- I'm not saying what you should do. I want recommendations. But some people could see value that as the standards change, having a special control that will require manufacturers to

revalidate perhaps analytically, or whatever means people think is appropriate, that in fact the performance of the assay, one, is not changed and, two, doesn't raise any concern about safety and effectiveness.

DR. BEAVIS: Yeah, this is Kathleen Beavis.

I keep going to Dr. Whitaker's Slide 17 that talks about postmarket surveillance, and that one recommendation, again, periodic, to be defined by you all, to demonstrate an absence of drift in assay performance and to confirm inclusivity, I think, is great. And I'm hoping that'll be considered by the other Panel members, too.

DR. MEYER: Yeah, Dan Meyer.

And the other term that I thought was useful that I've seen in some of the documents is to main substantial equivalence to currently available Class III devices.

MR. BRACCO: I just want to point out, from a manufacturer's perspective, postmarket studies are extremely difficult, extremely burdensome, difficult for industry and the FDA. And as Dr. Gitterman talked about earlier, the samples are difficult to obtain, and it just puts a considerable burden on the manufacturer.

DR. GITTERMAN: I find myself in the uncomfortable position of agreeing with Mr. Bracco. And I say that with a smile on my face, because of course, I agree with everything he said.

But I think a comment that was made earlier is that this shouldn't be a wish list. It should be sufficient and necessary. And, you know, it doesn't fall -- special controls don't fall into "it would be nice to have." It would be something that assures the continued safe and effective use of the device.

That much said, there are people who feel that there are certain, for lack of a better word, breakpoints or key points, for perhaps if the standard changes, that, you know, if an assay was originally the -- originally referenced against a certain standard, a new version

comes out, that might be a reasonable perspective. Or again, you know, certain critical clinical information.

But the idea that we'd like it or it makes us feel more comfortable would not be sufficient, in fact, to have a special control.

DR. SCHAENMAN: Joanna Schaenman.

Dr. Gitterman, I wanted to address your interesting question about cross-sectional versus longitudinal. I honestly don't have information on that, but I'm wondering whether Dr. Chou or Drs. Limaye and Cook maybe might be able to give us their opinion as to whether that would be necessary, the longitudinal sampling, or whether cross-sectional would be sufficient.

In addition, I wanted to go back to what Dr. Chou said about geographical diversity. Would that be beneficial at least within the United States? Would that be something that would be useful?

DR. GITTERMAN: We do mandate that. That's a given.

DR. SCHAENMAN: Okay.

DR. GITTERMAN: That's a given. Although people will argue how different is Cleveland from -- but the fact is that's -- there's a stock phrase, which I can't remember without an -- geographical and whatever diversity in every comment.

DR. SCHAENMAN: I think the answer today is pretty different around the United States.

DR. BEAVIS: This is Kathleen Beavis.

I understand that periodic postmarket studies are difficult to do. And maybe I've been doing this stuff for too long, but I still remember fairly acutely when there were issues with chlamydia testing. There was a strain detected. And there was a realization that one of the manufacturers was not able to detect it.

So, you know, by periodic -- that, to me, does not mean annual. That could be an every 20-year or, you know, however it is deemed, but it gives, I think, the Agency the latitude to be able to do it, if it becomes apparent that the assays that would be on the market are not able to detect what's circulating.

DR. PETTI: And I do have to agree with Dr. Beavis. Often, that responsibility actually -- it's a burdensome one, and it falls on all the clinical laboratories across the United States who are the ones that actually identify drift or inability to detect a new strain. So I do believe language for some kind of postmarket surveillance is important, especially when we're dealing with analytes like CMV.

DR. GITTERMAN: Just -- and again, I believe this exposes my ignorance. Is there something like a CAP proficiency panel or other ways that this can be done absent FDA regulation?

DR. BEAVIS: Okay. No, and I'll tell you why not.

DR. SCHAENMAN: Okay.

DR. BEAVIS: Because the CAP proficiency testing needs to get graded. And to grade something, you need to reach 80% consensus. So, as an example, if there's an STD instrument out there, and you know that *Neisseria lactamica* can give, you know, a false positive, speaking as somebody who was on the, you know, committee for several decades and chaired it for a long time, we're not going to send out *lactamica* because then we can't send out a gradable specimen.

And our colleagues in other branches of government want everything to be graded, and we get dinged if we send out something that can't be gradable.

DR. PETTI: And wasn't there a simple example in hepatitis C?

DR. BEAVIS: Several.

DR. PETTI: One of the genotypes.

DR. BEAVIS: Several. So there's a -- proficiency testing is just to make sure that -- it's not the same bar as educational and pushing possibilities, and it's a very different goal.

DR. GITTERMAN: Yeah. Our attempt to kick the can did not work.

DR. BADEN: Just --

DR. PETTI: We have a request to have Dr. Cook come back to the podium and address Dr. Schaenman's question.

If you need to repeat it, it's --

DR. SCHAENMAN: Yeah, and/or Dr. Limaye. I sort of feel like you guys provide a nice complement of virologic and clinical expertise.

UNIDENTIFIED SPEAKER: He ran away.

DR. PETTI: He can't have gotten far.

DR. SCHAENMAN: We'll have -- yeah. Yeah. But the question of serial testing versus cross-sectional.

DR. COOK: As it relates to?

DR. SCHAENMAN: Should that be mandated? Because I think that's a very intriguing question. I simply don't know the answer. I'm just curious what your expert recommendation would be on that.

DR. COOK: I think that as part of sort of the general performance of our assays, we get pretty good numbers about how an assay performs over time. So we, for example, make a control that we use for a year and a half at a time, and we expect it to stay in the same place the whole entire time.

And so we would hope that the performance of all the tests, whether they're LDTs or otherwise, for the commercial ones, we would expect that to be pretty consistent for a single sample over time. But it's very difficult to get enough of that sample the same way there -- that it is to try to get a standard. It just takes a lot of material. So when we do that,

we make a big batch of stuff and aliquot it. It takes all day long.

DR. SCHAENMAN: But I think the question, if I'm interpreting correctly, as raised by the FDA -- this is Joanna Schaenman again -- was taking the same patient over time and watching the evolution of their CMV viremia, or DNA-emia, as opposed to single samples. Am I interpreting your question correctly?

DR. GITTERMAN: Right. In response to treatment, that's exactly correct.

DR. COOK: Right. So I'm saying first, just -- you know, you have to know that your test isn't going up or down, otherwise your patient's going up and down and you're not even going to see it because it's just doing that.

But I think that we do serial studies when we're trying to look at new assays for the purpose of being able to see what the variation is and what's happening in an individual patient. So I do think that's probably important in a subset, particularly if you're looking at what's their --- you know, what's happening to the therapy. You're obviously going to have to do it in those cases.

But I did show you that one sort of patient sample that I'm not really clear whether it was a response to drug or whatever, but it just developed a sub-mutation at that one location where the primer set was. So, you know, these are viruses. They have the ability to make those kinds of changes. CMV isn't particularly variable, but I think that there is possibility that that happens with anything. So I think it's not unreasonable to do some samples, but how many? We don't know enough about CMV and how many genotypes there are and what parts we should really look at. So I think we don't know enough to really answer that question very well, I think. Sorry.

DR. ISON: So my only two cents is that -- thank you -- that I think that was a very elegant response.

But I think, given the rarity of mutations that develop during the course of therapy, it

would make more sense to kind of broadly collect a select group instead of just follow one patient over time, because if you do that, if you select, that's going to be a very challenging study to do. And the likelihood you find the one mutant in that select sample is going to be pretty unusual.

DR. COOK: Well, and just to add to that, I mean, we have a pretty good idea what the few drugs that you're using for CMV do to the virus, and we're busy, at least some of us, sequencing those areas. And so we have kind of an idea about what happens, but we don't know about random mutation elsewhere, where our primer sets might be.

Ajit, did you want to make a comment?

DR. CHOU: So, you know, with respect to whether we should use the same patient collected over time, or just simply a diverse collection of plasma samples from many different people, I would almost prefer a diversity of samples from different patients because they have more strains, and total variable loads have been mentioned repeatedly as being part of the calibration pool.

So we're really talking about two types of calibration. One is the internationally recognized standard, and the other one is to say that, you know, I would say some dozens of specimens, when they're trying to get something approved, would be needed to show that it's been duplicately tested with their proposed tests as well as, you know, one of the licensed ones, and just show how comparable they are. So I don't think it's important, for that purpose, to have serially collected from the same person.

DR. GREEN: Mike Green.

So I think where we're at, and we're defining the bullet about clinical performance studies, is -- and maybe it's method comparison studies as well -- is it looks like what we're saying is it would be nice to have some number of sequential, over time, patients, perhaps non-treatment, if they were available and willing to participate in study. It would be nice to

have a variety of specimens from a variety of different individuals, particularly if that showed a range of low, middle, high, and maybe non-detectable.

And then to what Dr. Gitterman said before, it could also include a panel of perhaps contrived specimens. I guess, in some way, the standard is a contrived specimen, but they could also be additional contrived specimens, where they try to take them to the different levels that you're at, so you're really getting a broad panel of testing of this assay against human specimens and laboratory specimens and internationally accepted standards.

DR. PETTI: Thank you. Are there any further comments? I'm soon going to summarize what we've been discussing.

MR. SIMON: Tom Simon.

DR. PETTI: Yes.

MR. SIMON: Just one question. What criteria would be -- what would be required from the patients, if they participated?

DR. GREEN: So in some ways, what might be happening is that when laboratories obtain these specimens, they don't use all of their sample every time they run it. And so if you were a participating center, you might have consented patients to allow use of your specimen once it's done, without any additional sticking of the specimen.

DR. PETTI: Mr. Bracco, as the Industry Representative, do you have any comments?

MR. BRACCO: I have no comment.

DR. PETTI: Dr. Flatau?

DR. FLATAU: No comment.

DR. PETTI: Okay. Mr. Simon?

MR. SIMON: No comment.

DR. PETTI: All right. So I will now attempt to summarize the wonderful discussion that we just had. And I'll try to do this in as a systematic way as possible.

So we'll start with Bullet Number 1. The Panel generally believes that recommendations for device labeling should include: The result generated requires interpretation by an expert, and this result should be interpreted in conjunction with clinical parameters, such as medical history and other various aspects.

And also in the label, repeat testing may be indicated, but we're not going to definitely prescribe repeat testing. And we are not going to necessarily specify a specific patient population in the labeling, meaning limited to a particular population.

Number 2, manufacturing information: I think we all agree that GMP compliance would be the recommendation. The method comparison studies, we all believe that has great value and that the comparator method would be decided by consensus experts, FDA. So it wouldn't necessarily prescribe what method that is.

Analytical studies, we referred to unfortunately Slide Number 13, as far as all of the analytical performance studies that need to be conducted. And we did add interference -- inhibitory study, inhibitory substances studies.

We also said, from clinical performance studies, that clinical testing done to a standard method would be advisable, and the specimens would consist of a diversity of specimens with various viral loads and different kinds of patient populations on various medications as well as a specific subset that would be sequential testing.

Dr. Green, in the analytic performance, there will be contrived specimens. That's part of what we do in analytical performance studies.

The calibration is a very important recommendation by the Panel. And we believe that it should be, that the assay should be calibrated to a globally accepted standard.

And then finally, postmarket surveillance to assess drift and inclusivity and also to evaluate that the IVD maintains substantial equivalence to the current standard.

I am going to pause there and ask the Panel if I misspoke or did not represent the

beliefs of the Panel.

Yes. Dr. Welch.

DR. WELCH: David Welch.

I wondered about one other thing under manufacturing information. According to an example given in Dr. Whitaker's presentation, it might be relevant just to talk about traceability to the WHO standard.

DR. PETTI: We can add that.

DR. GITTERMAN: We can specifically request that. Thank you.

DR. KOTTON: Camille Kotton.

I just wanted to consider, under device labeling, just including the whole discussion about plasma and that this is just for plasma and not for other specimen types.

DR. PETTI: The intended use will have the specimen type. Yes. It may or not be plasma, depending on the manufacturer's data that's submitted. Yes.

DR. KOTTON: Of course.

DR. PETTI: Thank you.

MR. BRACCO: I don't believe we had vehement agreement on a postmarket study, so --

DR. GITTERMAN: So no, I think the details remain to be discussed. I think the Committee is -- my sense is that they think there's value in it. But there's devil in the details, and I completely agree. But we've heard the Committee's certainly recommendation in that respect, without being exact, and the preference for such a thing.

Can I ask one -- oh, I'm sorry.

DR. PETTI: Dr. Hayden has a comment.

DR. GITTERMAN: Oh, I apologize.

DR. HAYDEN: Just again, under standardization, to include details of commutability

analysis and what method was used for that analysis.

And the other thing, just under manufacturing information, aside from, you know, what standard was used, and how traceability was established, it would be helpful -- and I don't know if it's the standard; it seems like I've had some package inserts where it's not included -- to have genetic target, because I think that could help users assess based on current information about diversity.

DR. PETTI: That's an excellent point. Yes. Thank you.

DR. GITTERMAN: I did have one, and I did not express this. And I do not want to delay this, so just a few opinions would be good. But how generalizable do people feel, in the context of diversity, between HSCT and solid organ transplant, in the context of simply the measurement of samples, such that we could generalize a little bit perhaps than requiring separate studies completely, in HSCT versus solid organ transplants? Hemologic malignancies versus solid organ transplants. It'd be -- just to get one opinion would be --

DR. PETTI: Dr. Baden.

DR. BADEN: Right. I don't see an issue generalizing between those two contexts. I think the issue was syndrome. And I think syndrome is a different issue that you have to push the applicant, because I think liver, eye, GI, may behave differently. I'm not sure HSCT verse SOT will be that big a difference.

DR. GITTERMAN: Right. So you would -- again, if we had measurements, we would, of course, want both, but that performance in SOTs would generalize somewhat to HSCT, and the reverse, instead of having to treat each one separately and increasing the burden on manufacturers. I see everybody nodding their head. It's between this and the break.

DR. CHOU: The interpretation of a given result differs in the patient populations, but the technical aspect is the same.

DR. GREEN: Can I -- and I -- maybe this inappropriate. So one of the growing uses in

the world of pediatrics of these is looking at congenital CMV and possibly following management of congenital CMV over time. So the labeling that we're proposing, is this limited to either transplant or immune-compromised hosts? Are we simply giving -- we proposing that a label would say that this would be a test for measuring the presence of CMV load in a particular compartmented serum or plasma?

DR. GITTERMAN: The answer is yes. We are discussing solely transplant.

DR. GREEN: Okay.

DR. GITTERMAN: Now, certainly, everybody, for a clinical need, would hope that manufacturers would come across with evidence to do so. Just the fact that people are comfortable with the measurement, someone takes it off the table -- and there's a lot of ways manufacturers could do this. We recognize difficulties, and we would welcome any manufacturer coming to us and trying to extend the indications for use. But right now, it would solely be labeled for transplant.

Very good question. Thank you.

DR. PETTI: Any further comments?

DR. BLUMBERG: Emily Blumberg.

Just pertinent to that, does that mean that there couldn't be a special control that said something about this assay in other populations? Because what happens typically in medicine is that something's released for some indication, and people are often off and running using it for others.

DR. GITTERMAN: That's off-label use. You're -- I hate to say this. It's completely off the table. But we would welcome --

DR. PETTI: Sufficient data.

DR. GITTERMAN: Right. Sufficient data for us to extend the labeling. And based on the discussions today, I think you've lowered the barrier to that substantially.

DR. PETTI: Dr. Gitterman, do you have the recommendations that you need and are adequate?

DR. GITTERMAN: I think this is, this could not be clearer, even though probably nobody around the table feels that way. This is --

(Laughter.)

DR. GITTERMAN: No. This is extremely, extremely helpful for us, and I can't thank you enough. And, you know, of course, this was the hard part. EBV and the others, that's trivial.

DR. PETTI: Great. So we will have a 10-minute break and reconvene at 2:40.

(Off the record at 2:28 p.m.)

(On the record at 2:44 p.m.)

DR. PETTI: We will now begin the benefit/risk discussion of EBV and BK viruses in transplant patients. Please take your seats.

Dr. Gitterman.

DR. GITTERMAN: So I'm going to try to be even quicker than I was this morning. EBV and BK virus, luckily we got through the really, really difficult issues this morning, now will be easy things to discuss.

What is the purpose of this? First, take a deep breath. Now you've taken a deep breath. Now, we're not going -- what we talked about this morning was to discuss a specific regulatory decision. That's not on the table right now, the reasons we're going to talk about. But we do want insight and expert opinion on just your general sense, your feeling. But there's no yes/no type of issues, even though the questions sound like it. We just want to hear people out. And there's a reason for that, as I'll talk about in a minute.

As you heard this morning, we have three classifications for all devices, including in vitro diagnostics: Class I, Class II, and Class III. I'm not sure why they didn't use A, B, and C,

but I, II, and III works. And devices can go up or down. You can't go down from I, and you'd go up from III, but the initial classification can be changed.

This is very, very uncommon because you have to -- almost an exceptionally good reason for doing so, but it does occur. And it occurs more often down from up. But a couple of years ago we did the molecular diagnostics for TB, which went from Class III to Class II. And more recently we did the rapid influenza tests, from Class I to Class II. So it can occur, but usually it's an uncommon circumstance.

Now, if a predicate -- and you heard a lot about that this morning, although we never strictly defined it, but a predicate, in 2 seconds or an, you know, extemporaneous definition, is a product that is currently marketed and cleared by FDA for which you compare yourself to as being substantially similar and equivalent.

If no predicate appears, you have a completely new analyte, a new virus, Zika virus, for lack of a better word, and there is not an FDA-approved or an FDA-cleared device, the test automatically becomes Class III. And that's what the guidance, in fact, says, automatic Class III classification.

However, of course, we all recognize that, in practice, that's not appropriate. And if the tests are low to moderate, that is, everybody recognizes, by which the sponsor as well as FDA recognizes, it should not be Class III but is more appropriate as Class II, the method we use is the de novo process. Now, you could consider this advanced regulation, so it won't be on the test.

So to be eligible for a de novo application, the submitter submits a test that he believes is appropriate for de novo classification. And again, with the submission, the sponsor would demonstrate that general and special controls is sufficient to provide a reasonable assurance of safety and effectiveness.

And if the sponsor's not sure, we have a pre-submission process where, in fact, we'll

give you that advice. So it should never be the case where a sponsor says, I don't know, and comes to us, and we say, no, you've got the classification wrong. It's usually well established before the actual submission. And, in fact, there's a regulatory process where we have to give you a guarantee of classification, but it's very rarely used, and it's -- I don't have to say -- almost always unnecessary. Rarely do we recommend it.

Now, for these specific analytes -- did I skip a slide? Again, there are no cleared EBV or BK virus. Hence, if they came in, with the pre-submission process, we generally would give them a recommendation. We'd say, well, it looks like your device may be appropriate for the 510(k) process -- or I apologize, would be equivalent to a 510(k), and therefore you should use the de novo process.

That's a very important discussion for sponsors. And it would be nice to get some input around the table, what people feel are the issues in that decision between a Class III and a Class II.

So what are we going to do? Just a few other points: Literature for EBV is exceptionally complex. This is not for the faint of heart. And again, recall that we're clearing a test for something. You're supposed to use it a certain way. Clinicians who read the label -- and I know we established that clinicians don't read the label, but those who do read the label, and I think Dr. Kotton said she has read labels.

Correct?

DR. KOTTON: Yes.

DR. GITTERMAN: So there is role model for the rest of us.

DR. KOTTON: I Google them.

DR. GITTERMAN: Okay.

DR. KOTTON: Camille Kotton.

DR. GITTERMAN: The --

(Laughter.)

DR. GITTERMAN: Oh, that's okay. You have tenure here. It's okay.

But again, labels have to describe how to use the test, who's supposed to use the test, what to test, when to test, and how to interpret the test. I mean, when someone develops a test, it's not to test something; it's to test something for a purpose. And again, for both EBV and BK, I want to hear this around the table, there is less certainty about clinical effectiveness, I would suggest. Perhaps this might be more true for EBV. And describing this in labeling and how people should use it may be extremely challenging.

Interassay variability poses even greater challenges in the setting of unclear clinical use and, again, is certainly -- could be a subject for discussion. But in certain ways, the treatment may be riskier because we know less about it and may be more likely reduction of immunosuppression. I'm just putting that out for discussion.

Now, from this morning's discussion, in times of uncertainty and a lot of information expanding, PMA standards offers greater FDA oversight. Each application can be looked at individually as more information knows. It may be challenging to identify special controls that are sufficient to provide reasonable assurance of safety and effectiveness in this case.

And again, even though this discussion came across this morning, and I think Mr. Bracco made exactly this point, once there are special controls, it's difficult to change once they're part of the regulation. Not impossible, but it's difficult. And again, specific instructions for use that can be channeled, as might be considered in a 510(k), may be difficult to work on.

So what's in the order of the day, again, are incredible projections for Dr. Limaye and Dr. Cook for giving us a, you know, giving us their input on EBV and BK. We recognize that time is very limited and that detailed discussion of questions for each virus will be difficult at best. Accordingly, we don't want answers. We just want to hear people's impressions

and general thoughts. And again, that's really what third part says. We really want to hear some general insight into this that can aid further discussions. Is that clear?

(Off microphone remark.)

DR. GITTERMAN: Thank you.

DR. PETTI: Thanks, Dr. Gitterman.

Dr. Ajit Limaye of the University of Washington will present the clinical aspects of EBV quant viral load testing and BK testing in transplant patients. We will reserve questions at the end of both speakers.

DR. LIMAYE: Okay. Well, the goal for the next 20 minutes is really to provide the clinical background and context for any discussion about how ultimately FDA might review viral load assays, specifically with regard to EBV and BKV associated clinical syndromes in transplantation. And as Dr. Gitterman alluded to, I think the complexity of EBV, in particular, is very high, whereas I would argue for BK virus, we actually -- that's one of the few clinical situations in which we actually have good clinical endpoints that can be used in conjunction with viral load assays that may not necessarily be the case for some of the other viruses.

So the primary -- although EBV can cause a number of clinical syndromes, the primary issue in transplantation is EBV-associated lymphoproliferative disease, or EBV-PTLD for short, which is an uncommon but very serious complication of transplantation. One of the difficulties in using viral load assays that I'll come back to is that the incidence of this complication, while serious, is extremely low. So no matter how good your test is, the positive predictive value, outside of a high-risk population, is always going to be very problematic, and I think that would be one of the take-home messages.

The fundamental issue, in terms of pathogenesis, is that there's an uncontrolled proliferation of latently EBV-infected lymphocytes, and that there is an association between

the amount of EBV detected and the risk of either having or ultimately progressing to PTLD. And we exploit this close link between EBV and the pathogenesis of PTLD and the viral load assays that I'm going to talk about.

As adults, virtually all of us, about 95% will have previously been exposed, infected, at risk for reactivation. Obviously, the situation is completely different in children, and I will come back to that in just a minute.

But primary risk factors vary between stem cell transplant and solid organ transplant patients, but in SOT, being a EBV-mismatch, being one of those rare 5% of people who are seronegative and at risk for primary infection, the risk is increased anywhere from 5- to 10-fold compared to seropositive patients. And then there is specific high-risk subpopulations within stem cell transplant, T-cell depleted and the use of ATG, that seems to increase the risk.

There are a number of challenges when we think about how to use EBV viral load assays in transplantation, and Dr. Cook, my colleague, is going to discuss in detail with you some of the assay-specific issues. But I think it's also important to remember a number of clinical issues, biological issues that have nothing to do with the assay.

First, as I alluded to, this is a very uncommon -- obviously serious but very uncommon, and so the positive predictive value, the specificity issues are quite significant when thinking about viral load assays for EBV. EBV, based on the number of latently infected B cells, is particularly prone to reactivate in immunosuppressed patients and again gets at this issue in complexity of specificity of these assays for predicting some clinical relevant outcome.

And then, although we use PTLD and EBV synonymously, there are reasonable data that 5, maybe up to 10% of cases of PTLD are, in fact, not related to EBV, and obviously, those wouldn't be in any way predicted by EBV assays.

And then finally, unlike the situation for CMV, where at least we have something --it's far from perfect, but we have antiviral agents with a proven track record, the agents that we have or strategies that we have, particularly when EBV monitoring is done to predict risk, are really not proven and/or not safe.

So the consensus and guideline recommendations, in general, my take on them for their use of EBV viral load assays for predicting risk, routine monitoring, are really based on much, much less data and, importantly, lower quality evidence than is the case for CMV.

And all of the guidelines generally agree, based on this very important risk factor of EBV serology, that both the donor and recipient's serology for EBV should be assessed pre-transplant. And then because of these limitations of specificity that I spoke of, EBV monitoring routinely to predict PTLD risk should really be focused on the highest risk subpopulations, such as some of those conditions that I've listed there.

So the specific uses of EBV viral load monitoring are listed here, one, to predict PTLD risk in a preemptive therapy approach, as we discussed for CMV. And that's typically recommended during the first 3 to 12 months. And again, the devil's in the details in terms of what level of viremia is considered significant. And in such patients who have whatever that significant viral load is, it's recommended uniformly across the guidelines that there be a detailed assessment for whether that patient might, in fact, have PTLD at that time, associated with significant EBV viremia, and then consideration given to various interventions. And probably the most available data relates to reductions in immunosuppression, but which agent, how much, all of these are important questions that there aren't really evidence-guided answers to.

And I think this uncertainty about EBV monitoring is reflected in clinical practices at transplant centers. The general sense is that pediatric centers use these assays more so than adults, partly related to the fact that they have higher proportions of patients at risk

based on EBV donor recipient mismatch. And then some of the other subgroups that I have listed here appear to be the groups in whom EBV routine monitoring, as a predictor for subsequent PTLD risk, is done most frequently.

Another use of EBV assays is as an adjunct to the diagnosis of PTLD. And all the guidelines are quite clear that this should never replace or substitute for critical data that's available in the biopsy, in terms of other molecular and other studies. But we're looking essentially for relative high viral loads that seem to be associated with the development or the presence, at that time, of PTLD. And a variety of studies have suggested that the sensitivity, again, depending on what sample type, what threshold is used, that the sensitivity for established PTLD is on the order of 80 to 90%.

But that clinically significant viral threshold, unfortunately, appears to be both assay-specific and specimen-specific. That raises important issues about how these assays are to be used.

Two other clinical uses of EBV viral load assays are monitoring response to therapy, again, exploiting this relationship between viral load of EBV and an outgrowth of uncontrolled replication of EBV-infected cells, such that patients who respond to therapy, typically there will be a concomitant reduction in viral load.

And conversely, in patients who either fail to respond or progress, that viral load remains elevated or increases during therapy. And then finally, there are fewer data still, that in a patient who establishes remission after treatment for PTLD, that monitoring might be useful in predicting risk of recurrence, although the basis in terms of data for that particular clinical use is really quite scant, in my view.

So, to summarize, I think, how we use EBV viral load assays is based on very limited, low-quality evidence and is widely variable across centers. If they are to be used, I think really focusing on the highest-risk populations is what makes sense. And my view is that

major work would be required in this field, both with regard to assays as well as clinical evidence, to really make sure that we could use these assays in a way that would positively impact clinical outcomes, which I'm not sure the data support currently.

All right, switching to my most favorite virus in the world is BK virus. No biases here. Beautiful biopsies of a patient with histologically proven BK virus nephropathy, or BKVN for short, which is the disease of interest.

And BK virus really has its greatest impact in kidney transplant patients, where it causes this entity of BK virus nephropathy. The overall incidence estimates are 1 to 5%. And once you have biopsy-confirmed disease, dozens of studies of large numbers of patients unequivocally point to premature graft loss in such patients. So it's clinically an extremely important situation in transplantation.

And there's something unique about the kidney allograft such that this is a problem in kidney transplant patients but not necessarily in patients who are intensively immunosuppressed but have their native kidney. And as a result, current recommendations for testing for viral load BKV are really restricted specifically to kidney transplant patients rather than other immunosuppressed solid organ transplant populations.

The disease with which BKV has been linked, and I'll say linked or associated rather than definitively proven, in my view, in stem cell transplant is completely different. It's hemorrhagic cystitis. And, in fact, hemorrhagic cystitis is distinctly unusual in solid organ transplant patients. And why that is, is unknown. But the data linking the viral load of BK virus to hemorrhagic cystitis is not nearly as well established as it is for BK virus nephropathy, and as a result, there are no recommendations for routine monitoring of stem cell transplant patients, only as an adjunct to biopsy in cases where BKV -- or hemorrhagic cystitis is suspected.

So just to illustrate the importance of BK virus as an emerging cause of graft

dysfunction, these are data from over 140,000 kidney transplant patients in the SRTR looking at two specific time periods, 2000 to 2004, and comparing the results to 2005 and 2010, looking at attributable causes of allograft loss. And things that have a -- are on the axis, that 1.00 here on the y-axis, means that the relative incidence of those as a cause of graft loss haven't changed.

And the key point to be made is virtually all of these causes of first year graft loss have either remained stable or decreased, except BK virus nephropathy, that the incidence has increased by 44% over these two periods, again, just highlighting the emergence of this as an important clinical problem in kidney transplantation.

And when thinking about the use of BK virus load assays, I think it's really important to understand, at least what we know today, about the pathogenesis of BK as a background to understanding who would you test, when would you test them, where would it matter that you diagnose people with BK infection, and that really requires some limited understanding of pathogenesis, which is far from fully understood.

Based on seroprevalence studies done in the 1980s, 90 to 100% of us, again, as adults, would have been previously exposed, infected. Autopsy studies using Southern blot hybridization show that we have BK virus latent in our renal tubular epithelial cells, as well as urothelial reservoirs, which becomes important when you think about assaying either blood or urine.

We can fairly efficiently reactivate BK virus from latency with immunosuppression. Thirty to fifty to seventy percent of patients will have detectable virus in their urine. And viral replication in the vast majority of patients, even who are immunosuppressed, ultimately is controlled by the immune system, and it never progresses. However, in the presence of various co-factors, and other as of yet not fully defined risk factors as second hits, low-grade viral reactivation, which is manifest as viruria, can progress to ever higher

level replication and ultimately result in the disease process at hand, namely BK virus nephropathy.

And fundamentally, there's two pathophysiologic processes that explain allograft dysfunction in the setting of BK virus nephropathy. And understanding what those are makes it much more understandable where, in the process of BK virus reactivation, it makes sense to intervene. And those two processes are interstitial nephritis and acute tubular injury or necrosis. And both of those are fundamentally reversible processes, whereas tubular atrophy and fibrosis are irreversible processes. And so that really places an emphasis on diagnosing BK virus infection early rather than late.

What we know about the natural history has now been defined in multiple prospective studies, and there seems to be a very systematic, step-wise progression between early reactivation that's detected in urine that probably results from renal tubular epithelial cell reactivation, combined with a component from the urothelial cell reservoir, all the way to higher grade viremia -- higher grade replication resulting in viremia and then ultimately the disease, or BK virus nephropathy, which is diagnosed by biopsy.

And these are the estimates of the incidence, cumulative incidence of each of these endpoints in patients who are prospectively monitored. And what's not evident here, but is very important to understanding how assays might be used, is that every single patient who develops BKVN, with almost undescribed exceptions, will have had preceding viremia. Every single patient who has viremia will have had preceding viruria. So there really is this very systematic, stepwise increase in viral replication and provides really the rationale for where in the process it might make sense to detect and quantify infection.

So what are the clinical uses in which one could envision using BKV-specific assays? Well, one is in the diagnosis of BKVN and as an adjunct to allograft biopsy. And there's excellent data suggesting that our so-called gold standard of biopsy to diagnose BK virus

nephropathy has major, major limitations. And I'll show you those data.

It can be used to monitor the course of established BKVN because we have good data suggesting that what we measure in the blood is reflective of what is present in the allograft. And so there's this very nice association that allows us to non-invasively assess what's happening in the target organ of interest.

And then finally, there are now guideline-based recommendations about routinely monitoring patients after kidney transplant as a way to identify patients at greatest risk, in whom preemptive therapies, reduction in immunosuppression could be used, and ultimately, maybe even prevent the disease of interest from developing.

So some centers, including ours, have reported that the incidence of biopsy-confirmed BKVN is actually decreasing with time. And so the good news is that's good. We're seeing less of the disease. The bad news is that diagnosis is now being made by blood viral load assays rather than biopsy. And I'll show you some data suggesting that in the modern era, only about 15% of cases of true BKVN are actually being diagnosed by allograft biopsy.

And the reasons that an assay -- that the gold standard for diagnosis is limited are listed there. First of all, from natural history studies, we know that BKV involvement of the renal allograft is extremely focal, almost stochastic, patchy, and involves the medulla first rather than later in the disease process. And the medulla is the least well sampled by allograft biopsy.

Second, in studies that did multiple core biopsies of the allograft, done by Cinthia Drachenberg, there was a 35% rate of discordance between one biopsy showing histologic changes consistent with BKVN, another biopsy saying there was no histologic evidence of BKVN, again, highlighting this patchy nature and how sampling more broadly, essentially blood, might give you more insight to what's going on in the allograft.

And there are good data suggesting that what we're measuring in the blood, but not necessarily in urine, is a result of what's happening in the allograft. And I'll just show you some data that address those points.

These are data from our center, about 700 kidney transplant patients, just simply looking at those who met a diagnosis of proven or probable BK virus nephropathy. And you can see that only about 15% of patients actually had an allograft biopsy that showed BK virus nephropathy. And the vast majority were simply diagnosed because of appropriate clinical setting and findings and the presence of high levels of BK virus in blood.

We have compared, and Dr. Cook will go over this data, looking at a gold standard of a positive biopsy, and found that the vast majority of such patients will, in fact, have viral loads greater than 10^4 or so, measurable in blood. And this was quite consistent between two separate lab assays.

Another way that we can use BK viral load assays is to monitor the course in patients who have confirmed BK virus nephropathy, and again, based on the premise that what we're measuring in blood reflects what's happening in the allograft. And it can be used to assessed whatever intervention, which is primarily reduction in immunosuppression. But importantly, this is where sample type matters. The biology is very different in terms of what we're measuring in urine compared to what we're measuring in blood.

And here are two concrete examples to illustrate those points. Here is a patient who had two consecutive allograft biopsies that demonstrated BK virus nephropathy. The blood viral load is shown in red. The urine viral load is shown in yellow. And despite reduction in immunosuppression, the patient's creatinine worsened. With reduction in immunosuppression, forget the intervention for a moment, here there were parallel reductions in viral load in urine and in blood. And only after BK virus was cleared from the allograft was there a clearance of BK virus from blood. And importantly, viruria persisted at

relatively high levels.

And again, this is illustrated in another case, which I'll skip for the sake of time, but what we're measuring is very different in blood than what we're measuring in urine, because urine likely reflects urothelial cell replication in addition to what's happening in the allograft.

We can also routinely screen patients post-transplant to identify patients at high risk of disease. And here, the premise is that earlier diagnosis because of the reversible processes of acute tubular injury and interstitial nephritis. And there is some data, at least, with various assumptions that may or may not be true, that it might be cost effective in specific populations.

But there are a lot of controversies about what sample to screen, what test to use, and that might better be reserved for the discussion period. But there are a number of international guidelines now that generally come to the same recommendation, which is that patients at risk should be screened, that screening should be more intensive in the early time after transplant, and that screening should continue for the first 1 to 2 years post-transplant, with differences with each of the specific guidelines.

All right. I'll end there and ask Dr. Cook to come up.

DR. COOK: All right. So I'm not going to show you more PCR amplification plots. What we're going to do is focus just on the things that are specific for either EBV or BK related to what we discussed this morning.

So I would just throw up here a slide with all the various kinds of things where we might want to measure EBV, so a very different sort of constellation of things where in the laboratory we might want to do this.

So our number one test is still transplant monitoring for this assay, but there are a large number of other things that we might want to do.

So just a quick reminder, primary infection, about 25 to 50% of peripheral blood memory cells become latently infected with the virus, which means that everyone pretty much in this room has a chronic infection. If we sampled your B cells, something like 1 cell out of 10^5 or 10^6 would be positive all the time, and they would be positive with something between 1 and 20 episomes per cell. So although these are transcriptionally quiescent, if we look with a PCR assay, we will see the presence of virus in those cells at all times.

So from the standardization issue, we can talk about sample type, we can talk about PCR design, and I'm going to talk about a couple of other things.

So, first, for sample type, this is an issue, both from the standard materials, what do we make the standard materials out of, and how many different ones do we need for all the different patient sample types.

So why do I say that about sample type? Well, EBV is very complicated from the standpoint of what you might be able to measure in the patient's cells. So in the upper left there, I've got a nice picture of an EBV virus. You might have intact, assembled, infectious virus. Underneath it, you can have DNA fragments. So these are usually termed liquid biopsies, or small DNA pieces, generally around 150 base pairs, and they are circulating around all the time.

Up on the upper right-hand side is the EBV genome, which can be episomes, and they are circular. And you can, as I described, have multiple copies in one B cell.

And then down below, you can have a linear version of that that you might see in like a tumor cell or something like that. So we're needing to measure a lot of different kinds of virus in its various sort of stages and configurations.

So how do we do that, and which is the best sample type to do that in? That's kind of the question. So here's a list of some of all the various kinds of things that have been tested. And there's probably -- this is not a comprehensive list. This is just things that, you

know, are pretty easily seen in the literature.

So why does that matter? Something even as simple as whole blood versus plasma is a constant argument. This is a comparison by one person who published in 2012 about whole blood versus PBMCs, whole blood versus BCs, so the white cells in the blood, plasma and whole blood. What we clearly know is a plasma -- measuring a plasma of the same patient that you're measuring whole blood will not give you the same answer most of the time.

Why is that? Because most people will have EBV in the cells, and you're going to measure that when you do a whole blood or a cellular compartment that you're not going to measure when you're doing the plasma, so not good agreement, much worse here than for CMV when we talk about whole blood versus plasma.

So not to show you this entire article, I'm not going to go through this whole entire thing, but this was just recommendations that were issued in 2008, talking about what's the best sample type depending on what disease you have. And if you look in the sort of the middle column, plasma or serum, some are the best ones, some are the worst ones. And so there's no real consensus of what type.

And so when it comes to the lab, and we say run EBV, we have no idea which thing we should look at, what sample type. Based on what disease you're looking at, we might want a different sample type.

So most people either just throw up their hands in the air or do whole blood, or throw up their hands in the air or do plasma. And they may or may not be the best sample type for the disease that you're looking for.

So just recently, for those of you who haven't seen this, over this summer there was an article published by some of our colleagues at Johns Hopkins, and they did a study that I still can't hardly believe. They compared 2,146 patient samples of doing PBMCs compared

to plasma. And these were all-comers diseases, anything that was ordered for an EBV test, regardless of what. They found 105 people during that time frame that had some sort of EBV-associated disease. And they concluded that plasma is much better correlated with the clinical diseases in patients. So if you haven't seen that article, you should take a look at. It's pretty impressive.

So what about EBV PCR design? What do we know about it? There, I could find no large primer comparison studies that have been published. So there's a few individual ones and an individual lab that compared two or three, but nothing really across labs in any kind of large things. So there's a lot of primer sets out there. I don't know if there's as many as there were for CMV, but there are not any good studies.

One thing I would bring to your attention is that some people -- these actually came out of Asia, where they are looking really hard at nasopharyngeal carcinoma and the ability to measure residual EBV that's released from cells. And they advocate the use of a primer in the IR1 gene, so that's a repetitive gene. It's not entirely clear how many copies, but most virus, in its native form, has about seven copies of the virus. So if you make a primer set to that repetitive region, you actually get seven signals out instead of one, so extremely sensitive. And that's currently what's being used in a lot of the good studies in Asia for nasopharyngeal carcinoma.

That test, however, like with all the other liquid biopsy things, there's a lot of issues related to stability of those small samples. Those are the example that I gave you that are the small, 150-base pair fragments. So that's a completely different sample type that I really haven't talked about before that they're using for nasopharyngeal carcinoma.

So this is an assay I did find from that particular group. And what you can see, in essence, is evidence on the right-hand side of individual samples that were positive for EBV when they used the IR1 gene, and negative when they used other single-copy genes as their

targets, so clearly more sensitive in those cases.

So this is another published paper kind of getting on the same issue, which is, if you use a smaller primer set, you're more likely to pick up pieces. So on the left-hand side, they've basically, in this particular thing, designed different size fragments of the EBV genome and then have several different primer sets that each are going to amplify those size fragments.

And on the right-hand side, in the bottom, what you can essentially see is that if you have a very small fragment and a very small PCR assay, you'll get essentially 100% detection, which was their sort of target. Whoops, that was bad.

And so if you look, however, at a slightly bigger primer set -- so as you go to the right, the primer sets get bigger and bigger, you see that less and less of what's in there is actually measured. So the idea would be that we need extremely small primer sets to pick up all the EBV that might be there.

This is another sample that essentially did the same kind of thing and found out, comparing two different primer sets, that the smaller one picked up 13% more patients that were positive in small levels, implying that small fragments of EBV are present in the plasma, and you have to have a smaller amplicon in order to be able to see them.

So what do we know about comparison studies? Not nearly as many published for EBV as there are for CMV. What do we know about what we use to compare it with? So there is an international standard, released about the same time that CMV was, so about 5 years old. We have some EBV plasma panels that are made from commercial preparations, and we have one vendor that makes actually purified DNA that we can use for EBV. And if you'd notice, the strains for those two, the WHO and this quantitated stuff, are the same strain.

So this is similar data to what I showed you before for CMV, really bad comparisons

between laboratories. In this particular study, these were transplant centers, and you can see two-, three-log spread also. This is a similar study with different cell types, and you can see the tremendous spread for that as well.

This is an example of a more, much more recent publication, 2014, trying to say whether or not it makes any difference if we standardize, so the top panel is what the results were like for a couple of different primer sets with unstandardized results. And then the bottom column, the B is after standardization. So you can see much better performance of this assay after they standardized the two assays against the WHO material, so evidence that that might work.

This is part of what I discussed earlier. This is a French study with 12 labs, and the same thing, only this was in whole blood. So the dotted boxes in each of those pairs is before the material was standardized, and the solid boxes on the other side for each of those particular samples were the results across the 12 labs. So these actually look much better than most of the other data and give us an indication that if we use the same assay, standardized exactly the same way, there is some hope that we might get the same answers.

So this is evidence from one study that if you take materials and spike them into whole blood, you can actually get pretty good results across several different assays. And so this is the best whole blood data that there is, in relationship to being able to use whole blood as opposed to plasma.

And then finally, I would just mention, there is a published study concerning nasopharyngeal carcinoma, where there were four labs internationally, studying, trying to figure out what the variables were for this testing. And they found all kinds of variables that are discussed at great length in that particular paper, if you're interested in looking at that.

So just a quick preview, then, about how well are we really doing. So I've pulled data from the CAP and the QCMD for the last couple of years, to show you what the data looks like. This is for four samples from the 2005 data. You can essentially see that on the right-hand side, there are two samples that are between 100 and 1,000 that are not picked up by a significant percentage of the labs, one by 40%, one by 20%. And if you look at the next column over, which is the range, you can see that the range of results that people are resulting is still 3 or 4 logs, so not significantly improved, slightly better for the IU/mL data than the copies per mL data, but not significantly improved compared to what we might hope.

This is the QCMD data. Some people result in IU/mL, some people result in copies per mL. You can see the IU/mL is slightly better, but the spread of all the data is still pretty significant.

All right, so now let's talk about BK virus a little bit. So BK is a little bit easier from the sample type. We pretty much do plasma or urine. Some people are doing whole blood, but most of the data that exists is about plasma.

One mention -- one thing to mention about urine is that often the urine values are very high, and so we have to worry about crossover contamination, sample to sample. And we also have to have an assay that's linear, extremely high.

So this was a paper from 2008, where Ajit came to us and said you keep missing positive samples. I can get a biopsy that's positive, and you're not picking it up. So we spent about a year and fixed our assay. And what you can see there is the left-hand side is with an internal-made standard, and the right-hand side is with Dunlop, which is sort of the reference strain. And those are a series of patients with different primer sets, so VP1, blah, blah, blah, those are all different primer sets. And what you can see is individual samples that run significantly lower with an individual primer set than they do with the average of

all the other primer sets.

So as we evaluated that carefully, we determined that the vast majority of those were a result of missing Genotypes III and IV. So over the last 5 or 10 years, it's developed that what we thought was one genotype actually turned out to be six. And the worldwide distribution of those genotypes is not the same. And so our particular study, we had some IIIs and some IVs, and we were pretty much under-quantifying them by a couple of logs, as you can see, and a couple of them were missed altogether.

So those little ones that are the dotted lines on the end are -- on the bottom of each of those little curves are ones we completely missed altogether with at least one of those primer sets. So your primer set is very important. And after we got this data, we made two really good primer sets and put them together, so our assay has two primer sets in it.

This is a similar kind of result from a European study from a more, much more recent study. And in this case, you can see there are outliers again that are low. And in this particular instance, it again was genotypes. And in this case, in the European group, it was Genotypes II and Genotype IV that they were failing, so a different distribution of genotypes in Europe than here, and they missed a different set of samples than what we did.

So very little cross-comparisons other than the data that I gave you. About 6 months ago, we were embarking on a study, and we wanted to know whether the clinical cutoff was the same for our assay compared to how it was originally published by Hirsch in Switzerland. And so we talked about sending a whole bunch of samples back and forth to compare with, but it was going to take an incredible amount of time to get the import permits and export permits and get everything to go back and forth. So we decided to look at the QCMD data. It's a quality control proficiency material that comes out of Britain. And so we asked them for the results for the last 2 years, and we plotted our results from the last 2 years.

On the left-hand side are our results and the Hirsch lab results, compared to the mean, for what was gotten by QCMD. You can see, in both case, we're pretty high, compared to what the mean was. But on the right-hand side, if we graph it against -- if we graph our assay against Hirsch's assay, we get almost a perfect correlation. So for whatever reason, almost everybody enrolled in this survey is running lower than the two assays that we were directly comparing against, by about a log.

So here are the QCMD results. This is similar to what I showed you before. The important thing is on the right-hand column, where there are a tremendous range of results that are being sent out, more than 2 or 3 logs again.

And so what is available for standardization? So standardization, the international standard for BK was released in January of this year. And so there's not much anything in the literature, so we have been studying it for a while. And so we got ahold of the WHO material and materials from a number of vendors. You can see the list of them all, including some sort of working, playing around stuff that NIST was doing, of two different varieties.

So if we used the WHO material, and we used it as the standard to calculate everyone else on all those other samples, we essentially got the correct results for everything. So there was really good agreement across all the different sample types coming from all those different sources.

However, we decided we wanted to quantify the results and see how the IU/mL compared to copies per mL. And so we ran digital PCR. For those of you who aren't familiar with it, all the positive ones for one primer set is on the right-hand side, so the top brown ones and the green ones are all the VP1 positive events. The ones on the top sides are the blue or the brown ones are all the ones that are positive for the T region. And it doesn't take very much looking to see that there was a lot more green ones than there are blue ones. So based on our calculations, we determined that there were about four or five times

more VP1-reactive events in there than T-reactive events.

So we thought there might be some sort of mismatch to our primer set, so we sequenced. And we just happened to have a next-gen sequencing machine we were playing around with, so we just threw it on there, did next-gen sequencing.

So what you see here is the coverage. So the line on the y-axis is the number of sequences that we found at each location. And what you can see is a very significant dip down with the blue line there, which is the WHO material, compared to the other lines, the sort of yellowish one and the red one, which are the NIST materials.

So our interpretation of this data is that the WHO material has a number of different subpopulations in it. We estimate at least nine or ten. And most of them have a very strong, very large dilution in the T region. So that gets back to this is a culture. Grew a whole bunch of it up. And they grow it in the presence of a mutation, cell line that has large T antigen in it. So as they grew it, basically it just stopped making T. So instead of having a 5.2 KB -- BK material, you have something that's more like 3.8 and missing a significant part of the genome.

So why does this matter? Most of the assays that are currently available in the laboratory are targeted to the T region. And so that would mean that we would probably over-quantify everything by about fourfold if we used this particular standard and a T-region assay.

So, for BK, the standard stuff is really sort of inadequate, not going to work, and we have a lot of work to do in order to fix the standardization of BK at this point.

So I'll stop there, and I guess we'll take questions.

DR. PETTI: Thank you, Dr. Cook and Dr. Limaye.

Does anyone in the Panel have a brief, clarifying question for either Dr. Cook or Dr. Limaye?

DR. WELCH: Dr. Cook, what specimen types do you use in your own lab for EBV? Just whole blood or plasma?

DR. COOK: We use plasma.

DR. WELCH: Okay. You've always used plasma?

DR. COOK: Yes. And we do a fair -- well, it's something we haven't talked about. We do a fair amount of spinal fluid as well.

DR. WELCH: Okay.

DR. COOK: So, for EBV-associated neurologic diseases, but we monitor something like, what is it Ajit, something like 10 or 15% of transplants are monitored for EBV, as opposed to something like 70 or 80 for CMV. Correct me if I'm lying here. And so we do a fair amount of transplant monitoring with EBV, and those are all plasma. And almost everything else we do is spinal fluid. We also do a fair amount of tissue, which is a totally different situation.

DR. WELCH: Okay, thanks.

DR. COOK: You're welcome.

DR. GREEN: So as the pediatrician at the table -- or there's two, because Randy's over there -- I just want to make a clarification that, you know, that we're interested in not only diagnosing PTLD. In my mind, EBV disease is as important in these populations to diagnose as PTLD. And, in fact, if you think of it as a spectrum of disease that progresses over time, the goal would be to get it while it's disease and before it's PTLD.

And, in fact, the other thing to consider, if you were really doing preemptive strategies -- and I've really come to this crystallization just recently, and those of you in the room know that I've thought about EBV loads going back to when they started doing them in the early 1990s -- is that one thing for the Panel to consider is while you will probably have better specificity if you use sample plasma, if you're using this load as a strategy to

inform a preemptive intervention, you will, by definition, be preempting at a much later time when you get to the point that you can detect it in plasma as opposed to detecting it in EBV load.

And so while all the caveats of interpretation that we talked about for CMV, and maybe a log or three more, are in place, in fact, only detecting it in plasma limits the utility of the test and probably means that if you're going to do a preemptive strategy to prevent disease, you're going to be less effective than if you used a whole blood or PBL-based assay.

DR. BADEN: The detection strategy for EBV differentiates latent versus lytic virus?

DR. COOK: No. No, not at all. We're just looking for the presence or absence of the virus.

DR. SCHAENMAN: Joanna Schaenman.

Thank you both for those presentations. Those were excellent. You really boiled down a complex situation quickly.

I had a question for you regarding BK virus. I think that the information that you presented regarding the WHO strain is certainly concerning. I guess my question is in your expert opinion, has your primer strategy overcome the problem of strain diversity?

DR. COOK: Well, we hope so. We haven't, to my knowledge, had any more biopsies that are positive that we've missed. But it's a numbers game. It's a function of how much diversity do you have and how many do you have in your population.

So after we got done, we made two primer sets that matched every single sequence we could find in GenBank at the time. And then we sat down and talked about should we run the assay for a couple of years and run both primer sets to see how often either one of them missed. And then we figured out how much manpower that would take and decided it was more trouble than it was worth. And so it's hard to know because you don't know what diversity you have in your population until you miss one, and then you can kind of do

that.

So we hope our primer set's picking up everything. We made it into two -- in two very consistent areas that should not have a lot of variation. But there's no way to know until you miss one, so --

We do have people who are sending us samples, as a result of that paper, from all over the country who have missed BK, and we have picked every one up so far. But that doesn't -- you know, that's not an end of everything. That's just random samples that --

DR. SCHAENMAN: Got you.

DR. COOK: -- people have sent to us.

DR. SCHAENMAN: So maybe, to summarize, with this proactive approach, the problem of strain diversity can be addressed. Is that a fair statement?

DR. COOK: Yes. Yes. Well, and as you can see, we can separate them out and look at them and see how they behave. But you don't know you're missing until you miss, so it's extremely difficult to -- you have to set something, some sort of monitoring system in place, like the commercial labs have for HIV and HPV and HCV, before you really understand.

So we're a long ways from knowing enough about diversity, I think, for all three of these viruses to really understand that, but for BK in particular. So there are less than 100 full-length sequences for BK in GenBank, and that's not anywhere near enough to be able to decide how much diversity we have throughout the whole world.

DR. ISON: So that's, I think, the most concerning thing you've said all day, for such a common disease, that we have very limited data. Are you using a single or dual primer set for your detection of BK?

DR. COOK: We're using a dual, and it's the same color. So either one of them give us amplification that we hope is approximately the same quantitatively.

DR. ISON: So given some of the challenges with the WHO standard, would you feel

that it's especially important for BK assays to be dual primer?

DR. COOK: I would say that it's probably more important for any virus that has a lot of variation or if you're making your primer set in an area that you would expect some variation. So if you're making it into a, you know, a surface protein that might change, than you probably had better worry about it more than if you're making it against something that you would expect to be more constrained.

DR. BADEN: Cross-reactivity with other polyomaviruses, as we seem to be going to higher and higher numbers, polyoma viral types --

DR. COOK: Yeah. However many we're up to right now. We have really only tested with JC, which it does not react at all with JC. If you're familiar with the older literature, the older primer set actually was perfectly good at picking both JC and BK. We don't have really access to any of the others, so we haven't really tested them in a laboratory, but you can obviously do GenBank searches and see, and we would not expect them to react with any of the other polyomaviruses.

And we deliberately made it that way, so that it was very different than JC, because we wanted to be able to separate them.

DR. PETTI: Thank you.

DR. COOK: Thank you.

DR. PETTI: We now proceed with the second Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. We have had no requests to speak during this session, but I'll just pause and make sure.

Does anyone want to address the Panel at this time? Yes. We have one individual who would like to address the panel. So Ms. Asefa will now read the Open Public Hearing disclosure process statement.

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

DR. PETTI: Please come to the microphone. State your name, company, and any financial disclosures. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of your presentation. And you will have 3 to 5 minutes.

DR. HO: Okay. Great. Thank you. My name is Shiaolan Ho. I work for Abbott. So I'm Abbott employee. My trip is financed by Abbott. I don't have any other disclosure beyond that.

I'd like to thank the Panel and the speakers.

I have two questions. The first question is about the use of the assays we discussed, CMV, EBV, BK, and maybe additional transplant markers, whether you see any difference in terms of their use for pediatric population versus maybe, you know, adult population. And I guess the follow-up question is if there is no difference, then would FDA advise a labeling to not be restrictive to a specific population? So that's first question.

And the second question I have is the assays, other than CMV, now we do not have FDA-approved assays, and if we -- I am just anticipating where discussion is going. If the Panel agrees on a de novo approach for many of these markers, since there's no approved test, the de novo 510(k), I think it would be extremely helpful if the Panel could provide some guidance as to methods to demonstrate clinical performance, or whether there is perhaps opportunity to utilize a well-documented LDT as a comparator for maybe that first FDA-cleared assay. So that's my second question.

I think it would be extremely helpful to have that kind of guidance, so at least the first, the company with the first assay would have a relatively clear path forward. I think that would facilitate -- lower the burden and facilitate the development of our assays.

Thank you.

DR. PETTI: Thank you. We will incorporate those comments while we deliberate. And we will -- but we won't necessarily address the answers to those questions right now.

DR. HO: Great. Thank you.

DR. PETTI: Do you have any further comments?

DR. HO: No. That's it.

DR. PETTI: Thank you.

DR. HO: Thank you very much.

DR. PETTI: Thank you.

Anyone else wish to address the Panel?

(No response.)

DR. PETTI: I now pronounce the Open Public Hearing to be officially closed. We will proceed with today's agenda.

I open the floor to the experts around the table to begin deliberating on any issues that you may have with any of the data you have heard today, either in the Panel

presentations, the discussions with the FDA, or the material that you have read in your packets.

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

And so now, at this point in time, as you know, there are really no formal questions asked of us. But we are here really to use our expertise to provide guidance to the FDA on how we might want to classify these particular transplant-associated viruses. And --

Yes, Dr. Gitterman.

DR. GITTERMAN: I apologize. Actually, in response to some comments, we did put down on the handout -- it's the very last slide, if everybody has it in front of us, if --

DR. PETTI: Yes. On Page 8.

DR. GITTERMAN: Okay. I'm sorry.

DR. PETTI: Yes. Yes. It's in front of me. So I was -- yeah.

DR. GITTERMAN: Oh, I apologize.

DR. PETTI: Yeah. And the points to consider and what should be considered in making these decisions. And the first is what are the benefits and risks from diagnostics for EBV and BK virus, and is there sufficient information available to use these tests safely, or are more studies needed?

And finally, are special controls a consideration for either EBV or BK virus?

And I open this up to our panel.

DR. ISON: So I'll kick it off. So I think that, from my perspective, I'm going to think of them as two separate viruses. I think, with regard to BK, as was well summarized by our two speakers, there is a huge body of work looking at the predictability of viral load testing.

And so I think that, you know, getting to the first question, I do think that the risk

information about BK would allow us to consider having it as a Class II agent because I think that you could develop appropriate special controls for BK to allow that status to be granted.

For EBV, I think, as was clearly outlined, I think that part of the challenges is that there are some limitations to the data, at least as reviewed. And again, from my experience, you know, what's the limit of detection, which I think is a real problem with many of the assays that are either lab-developed or whatnot, where you have a lot variability at the limit of detection. And so knowing, you know, how low to go, in some regards, I think, is not as well defined. And therefore, I think a little bit more information would be needed, in my opinion, to grant Class II status.

DR. PETTI: Yes?

DR. BADEN: Just to clarify the process, Dr. Gitterman, if there is no approved or cleared predicate device, then the de novo 510(k) is using the predicate as sort of the current standard for diagnosis? And then your question is can a novel diagnostic approach do the de novo 510(k) without a simple, a direct predicate?

DR. GITTERMAN: It's a complex question, so if I confuse you, please point this out. But the goal of classifying, it's very similar to what was discussed this morning. The idea is that the risks could be mitigated, since that you've used the de novo process. And when the de novo process is done, we'd be able to write special controls such that the next manufacturer could do so.

Now, what would go in that initial evaluation? You could have whatever evidence the sponsor tries to put together in a package in his talk to us, in a submission that looks adequate. And if they have, let's say, an example assay that was thought to be a very good test that was not FDA-cleared, it was something abroad, and said we have clinical evidence to support this, we'll do additional evidence with our assay. These are all the ways we've

addressed inclusivity, reactivity, primers, etc., etc., etc. Then conceivably, what the appropriate LOD is and how to label it and how it can be safely used, then in fact, you know, if we thought we could write special controls after that, then we could.

The flip side of that, of course, would be the PMA approach, which again, has some drawbacks but also offers a flexibility that, as we learn more and we gain experience, we don't feel more rigid to say, yes, you as the next one should do this, this, and this. We could retain it as a PMA until the point we feel there's enough information evolved, similar, I guess, to CMV, to say now it's at that point.

There's also -- now, I would want to clarify. I think a lot of people have talked about the burden of clinical trials. And actually, there's some literature to support that, that perhaps the most expensive part of development is clinical trials.

Now, again, depending on what information is in the literature, the ability that a given assay would, in fact, relate to that, you know, would in fact be support of it, there's options like expedited access program, etc., where information -- where a sponsor can gain that information over time, postmarketing and supported, which to some extent, sometime -- you know, somehow gives you the best of all worlds, you could say, what's not known, if again, a product does qualify for that.

So the issue is based on what's known now, and the sponsor would make a proposal, and they could say, we could do this, we could do this, we could do this, and we feel those can be converted, that they would be a generalization that could apply to future assays, then in fact, the de novo pathway is correct.

Because when the de novo was done, that means it can be predicate assay. So the future assays in that the way they did it, could, you know, if it could be written down with special controls, would then be a guide to other companies to do so.

And that -- does that explain it?

DR. BADEN: So it's a de novo without a predicate?

DR. GITTERMAN: Correct.

DR. BADEN: And it becomes the predicate?

DR. GITTERMAN: It becomes the predicate and special controls --

DR. BADEN: Sure.

DR. GITTERMAN: -- based on our knowledge at that time.

DR. GREEN: Mike Green.

So I'm looking for a little clarification. Does something being approved, either through a de novo Class II or even through the Class III as a viral load, require that the clinical knowledge of how to use that result is absolutely known? Or does it require that you can get a result that is reproducible over time, etc. and so on? So is it about knowing how to use the test as opposed to the performance of the test and giving you the same result if you measure it in the same compartment on seven different days at seven different laboratories?

DR. GITTERMAN: And the answer would be the former. We would expect there would be an indication for use. We do not expect to approve a lab and then expect everybody to go through the literature and figure out what the right way to use it and interpret it and understand it.

Just parenthetically, I'd give an anecdote for that. We got a viral -- an EBV CSF assay, and the fellow says, wow, it's 300, and without having any clue what, in fact, that meant. So the fact is you have to have it. There are a lot of things out there that can be measured. And, you know, companies can promote it, different ways to use it. And if nobody understands it enough to use it properly, that's a significant risk.

DR. GREEN: Just to clarify, then, does it require the pre-existing understanding of globally accepted breakpoints? Or if it was compared, as you sort of mentioned, to an

existing laboratory-developed test, where retrospective use of the assay over time has sort of generated understanding of breakpoints?

Because again, in the absence of any test and any pharmaceutical support for doing these trials, and with only the more recent availability of the WHO standard, and also what I think is probably the case is that there is a more delayed introduction of the EBV standard, while labs are sort of introducing the CMV standard, that, you know, those data sort of across centers are not available, and there's a lot of variability, particularly because there's more compartment variability as opposed to, if you were to interrogate me, I would tell you that I think I have a pretty good understanding how to use results from my assay in a variety of different circumstances, in a variety of different populations, at my institution, based upon my experience, some of which we've published.

DR. GITTERMAN: And I think that's a very good question. I would suggest the 2013 guidelines for CMV don't suggest a specific breakpoint.

The question is -- and there are degrees and degrees, but fundamentally, our mission is to help everybody. We are not trying to hold anything back. But as long as there is a way to reasonably describe it, so that a reasonable person could use it reasonably, then, in fact, it doesn't have to have every "i" dotted and every "t" crossed. But if people are uncertain about which matrix to use, what levels to use, how to use it and what to measure, how to interpret the measurements, it's not really a very, you know, a very good assay, in a lot of ways.

But again, there's levels and there's levels. We can certainly, through expedited access -- I know I've mentioned that several times, have means under the PMA to, in fact, you know, allow something to be a little earlier than we normally would, yet feel it's relatively safe to use.

I should also mention, too, there -- the PMA does have a terrible connotation. And

sponsors in the room immediately say PMA, it's off the table. But the fact is we are reasonable. And we can do things within a PMA paradigm that do not have to be so perceived as, you know, as extreme, and deal breakers. We really do want to talk to people and understand it.

But again, and I will just say, these two examples do pose challenges to the 510(k) paradigm because, as opposed to CMV, you know, they are, you know, they are -- how would I -- I can't describe it. Obviously, far less is known in the treatment. Everything is -- there's much greater risks to the potential use in that way because so much less is known. And exactly as you said, without knowing how an assay responds to immunosuppression, or more importantly, reduction of immunosuppression, we might be doing some bad things to patients in certain respects without really good understanding.

So but -- and I -- one of the initiatives of the center, for last year and always, is to incorporate literature. We do not expect sponsors to generate every bit of knowledge from scratch. You know, again, literature, other reasonable information could be used to leverage what a sponsor has to do. But the fundamental question of how to use the assay is -- really the question has to be resolved prior to -- it has to be labeled.

MR. BRACCO: You bring up a good point, though, about the clinical validity. And I think the bar is somewhat higher in the PMA world. You know, by default, 510(k) devices are already out there. And very few questions are asked about the validity of those devices.

When you bring a new device in through a de novo, and then you have nothing out there, and obviously, that's a question that's going to be asked. But I think the bar is going to be much lower on the 510(k) side -- still be asked but lower than the PMA side, if I'm correct.

DR. GITTERMAN: Well, again, and I do not want to be the only person talking, I would perhaps disagree with you in the sense the reason the bar's lower on the 510(k) side

is because so much is known. I mean, it's always safety and effectiveness. I do think, again, that -- I don't want to be a shill for the EAP program, but we really do want to listen. All of you are experts, and in fact, if I heard agents' disclosures correctly, so we have a consultant, which is a very valuable activity to companies.

And again, you know, we certainly encourage that, in a sense, is manufacturers who do want to get in the space, and it is still question. There's a need for assays like this, to approach and to say what's an acceptable standard for clinical evidence? What would we do? What do we have, what can we generalize, etc.? We would welcome, you know, expert opinion to decide whether there's a pathway forward.

And again, we certainly welcome manufacturers to approach us and say do we think this is enough for a PMA, or do we think they could do this under EAP, or do we think a de novo pathway is correct? And certainly I think part of what we want to hear today is really embodied in those two questions. You know, really, what is your sense of is there enough known to say, yeah, there really is a lot known, they could give pretty straightforward guidance of what a sponsor should do, or do we need to look at this carefully. And it's evolving, and there's a lot -- knowing that, we really want that flexibility, that might be more appropriate for a PMA at this point until we know more.

I think, I have to say, I can't thank Drs. Limaye and Cook, because I think in a very short presentation they were able to highlight there are a lot of known unknown -- well, I can't really -- there is certainly a lot of unknown unknowns, to say the least. And, you know, there are some known knowns. So please.

DR. PETTI: I think maybe we can break down this discussion into first, BK, since Dr. Ison has already kicked that off, that he believes that there's sufficient data to support a de novo 510 classification. And perhaps we can just go around the table.

And I'll start with you, Dr. Kotton, rather than our Industry or Patient Reps.

DR. KOTTON: So in thinking this over, I do think it's really important that we actually have an FDA-approved BK assay. There are an estimated 18,000 kidney transplant patients a year in the United States, who periodically, during the first 2 years after transplant, as per the nicely summarized international guidelines and other -- there are numerous guidelines that recommend screening in the first 2 years after transplant.

So each of them have roughly 10 assays -- depends on the details of the protocol for screening. But certainly we definitely use this assay. It is recommended. And it's chaos as far as what we send and what we get for results. You know, the results, there's no currently utilized international standard. The results are kind of all over the place. Sometimes I get results from Quest. Sometimes I get them from Mayo. I mean, who -- and they're not comparable. And then the nephrologists are really struggling with that.

And so this is kind of a really random assay that we send that's recommended, but then there's sort of no control over the current assay we have. So I actually would say it's pretty imperative to get something that's much more controlled and hopefully would be FDA approved.

So that being said, I do think that I would agree with Dr. Ison that there is enough data on BK such that I think with this could potentially be a Class II.

DR. BLUMBERG: Yeah. I agree with that. The thing that's sort of interesting to me is I think we are very accustomed to using BK viral load assays and sort of feel like we know what it -- the information it gives us. But I was impressed today that I actually learned some new things in terms of strain diversity that I actually had not really appreciated. And so I think that there will need to be definite, you know, special considerations for this because it's not quite as straightforward.

I think the other thing about BK that struck me is there is at least one commercial assay that's pretty widely used. And so I think there's data of variable quality but

associated with a particular assay, and fewer people are doing lab-derived testing for that than I think is going on with BK, and that also makes the situation a little bit different for EBV and BK.

DR. ISON: So, yeah. I mean, I tend to agree, at least in terms of the development of the clinical data indications for use, that, you know, BK is sort of more mature. We could talk about EBV, of course, separately. There are clearly some technical challenges, perhaps more so with BK, but it does seem that we could encompass those sufficiently with special considerations as they -- you know, that this could be safe and effective for use, so --

But the strain diversity issue, the sort of lack of maturity/issues with the WHO standard as it sits now, need further work, and that would probably, you know, have to be part of the process.

DR. PEREIRA: Yeah. I agree that probably Class -- de novo Class II seems reasonable, given the information that we have and the risks of BK testing. One thing that's sort of important perhaps to consider is if we create sort of special controls, is that with newer therapies of direct antiviral therapies, I'm thinking brincidofovir, coming into the market in the next few years, hopefully -- you know, so therapy, monitoring of therapy might be something to put there as sort of a marker also, in the approval perhaps or monitoring.

DR. WELCH: Dave Welch.

I also agree with going forward on a recommendation for the de novo for BK. And the main thing that seems to be different between that and CMV is lack of the reliable WHO standard, but if I understood Dr. Cook's presentation on the digital PCR, many of the other commercial sources are good in their characteristics, and maybe something could be chosen from those.

DR. SCHAENMAN: Joanna Schaenman.

I appreciate the recommendation to consider these viruses separately. And I also

want to thank the FDA for targeting BK virus at all. I want to chime in with what Dr. Kotton said is that this is sometimes an unappreciated virus that is, however, a big part of modern transplant kidney care, and it's really been lacking that we haven't had a more reliable test.

I also want to agree what others have said, that I do think there's sufficient information, thanks in large part to the work of Dr. Limaye as well as his colleague and collaborator, Dr. Hirsch, in terms, I think, that we can intelligently design the special controls for this particular virus, and I think it would be a real benefit to the field.

I guess the question is should we use, as was brought up, one of the laboratory-developed tests as a example or the current commercial available test? I mean, I'd welcome Dr. Cook and Dr. Limaye's input on that. But nonetheless, I think that we're within striking distance enough that Class II would be very appropriate and a real benefit to patient care.

And the last thing I wanted to say was that if one feels that maybe yes, maybe no, are we there in terms of sufficient information, I think that, although we all agree that it's a huge burden and causes a lot of patient suffering and just sort of wasted organs because of loss of organ function, I don't think it meets the burden of life-threatening/sustaining, etc., or causing a potential unreasonable risk.

So even if you're looking -- going back to the flowchart that was presented to us this morning, if you're on the fence about sufficient information, I think that BK is at least half a log less threatening to life compared to CMV or perhaps EBV. So I think we should feel comfortable on both accounts, that we have more information and it's less of a life-threatening disease, to go strongly with a Class II recommendation.

DR. BEAVIS: This is Kathleen Beavis.

I agree with what was just said.

DR. MEYER: Dan Meyer.

I also agree. I was surprised when I read through some of the information, that like BK, there was no FDA-approved assay. It was kind of surprising to me. But I agree with the consensus.

DR. LA HOZ: This is Ricardo La Hoz.

I agree with the de novo to Class II classification.

DR. CHOU: So Sunwen Chou.

I guess I'm going to, you know, express a slightly different opinion here. I think suddenly there's a lot of clinical demand for the assay, and there's no question that it's high priority. But I do feel that a lot of major important, you can even say fundamental, aspects of the quantitative assays are underdeveloped at this time, beginning with the issue of the calibrating standard, which, you know, from what we hear is clearly a defective standard.

First of all, you know, there is no business of any international standard actually missing parts of the genome. That's pretty shocking. And, you know, it also needs to fairly represent a reasonable diversity of sequences and so on. Remember, this is a tiny genome compared with CMV, and there really should be a, you know, serious effort to go represent the diversity of strains in that calibrating standard.

And similarly, with primers, you know, if it's like a needle in haystack to search for the primers that don't suffer from strain variation, that's a huge amount of development work. And also the clinical validation of the assay is something that likewise requires a lot more data. That is, what are the actionable loads, and what patient populations do we apply those to? Those are all things that need more data as well.

And then in terms of, you know, the risk to health and well-being and so on, that's part of the definition of importance of regulation. I'd say that if the assay returns misleading information that causes people to manipulate immunosuppression in an adverse manner, that's a serious risk.

So I think, for all these reasons, I'm more inclined to stick with a PMA as the more conservative regulatory approach, although I guess I'm not so aware of the nuances of, you know, what, you know, truly is the difference between this de novo II and a PMA.

DR. BADEN: As a card-carrying infectious disease doc, my answer is always, "It depends." So I can see the value of the de novo Class II, and I think there is a potential path there. But I also have some concerns because there are too many unknowns.

The issue of the gold standard for diagnosis, even though if there's not a predicate, how one establishes some predicate equivalent, the issue of host disease syndrome in that in the hematopoietic stem cell transplant population, 50% of patients in the first month after transplant will reactivate BK. A small percentage will go on to hemorrhagic cystitis. And it can be detected in the blood compartment, the urine compartment, and it doesn't necessarily portend poorly and can then be controlled through host reconstitution.

So there are different scenarios where one may look for this. And then the issue of treatment was alluded to, or immunosuppression manipulation, which I think, have unknown risks. And so one, it would have to depend on the circumstance that emerged, as to whether the Class III versus Class II seemed appropriate.

If the question is, is a de novo Class II possible? I think, yes. But it will depend on the details. And some of those issues would have to be considered depending on the proposed application.

DR. GREEN: Mike Green.

So I'm sort of a mind, a little bit, with Lindsey here. So in contrast to the CMV presentation that we saw before, we have no pre-existing FDA-approved comparator, and we have no acceptable international standard. We don't know whether we'd be talking about limiting this to just looking at blood or looking at urine, because some people use both, and it depends on the patient population.

And I guess we would probably be thinking primarily of only end organ transplantation as opposed to stem cell, thinking about it. You're only talking about kidney patients and not talking about other organ patients in whom the natural history is not well understood. But you might find loads and not have any idea what it means, although they rarely progress.

Having said that, you know, many, many, many centers here are testing for BK. And while perhaps I underestimated the number of centers that have gone to FDA-approved CMV assay, none of us are using, I think, an FDA-approved BKV assay.

And so getting some standardization imposed by the potential of using an approved assay really is important and attractive, and providing some sort of incentive to industry, because we've been doing BK measurements for quite a while, and there isn't an assay that's gone and been approved as of this time. And whether that's because of the Class III barrier, which maybe perception is that it would be much easier to go to Class II, and I don't really understand the expedited access and how that might sort of make the differences between these two processes be relatively manageable.

So I do think that there is probably a lot less confusion about interpretation of risk and result in this scenario than the second virus we're going to talk about. I'm not absolutely certain that we should say Class II versus Class III, but a lot of that would be based upon what the special rules were that we might describe or the FDA might generate.

DR. PETTI: Thank you, Dr. Green. And since you are our resident pediatrician on the panel, would you please comment if there are particular issues that are unique to the pediatric population that we might need to address, as opposed to adults, when it comes to these kinds of non-transplant viruses? I mean --

DR. GREEN: So we'll talk about BKV first. And I'm going to -- we'll save the EBV for the EBV discussion.

So I think, certainly, the potential difference is that you're more likely to see a primary infection in a child than you are in an adult, although the bulk of BKV infections probably happen in the first 4 or 5 years. And if we're looking at the kidney transplant population, there aren't a lot of them getting their kidney transplants at that time.

Other than that, though, to my knowledge, you know, the fact that having it in the blood happens before you have it in the kidney, or simultaneously, where you have subclinical kidney involvement, is the same in kids as in adults. I think the measurement, in association with hemorrhagic cystitis in a stem cell patient, is being in the urine and the blood and probably -- or possibly resolving despite whatever you do or don't do, as Dr. Baden said, is probably also the same.

So I don't think there are unique issues with this virus, other than the fact that you could see primary infection. And perhaps that might be at a different level, but I'm not sure that that really makes a difference.

DR. PETTI: Thank you.

DR. GITTERMAN: Again -- first of all, let me apologize to the Committee. I think it would have been -- and unfortunately is learned late in life, but it certainly would have been very valuable to have discussed what the expedited access pathway is and perhaps have presented that as, you know, less of a stark contrast between PMA and 510(k). I think, in this context, it would have been extremely valuable.

Can I summarize for a quick second what I heard? What I'm hearing very clearly that there's an essential medical need for this within the transplant community, and that the absence -- what I sort of internalized was the Wild West out there -- have to do that. And to have an FDA-cleared/approved assay, which at least had the -- I won't say mythological aspects, would have the analytical aspects that either a 510(k) or a PMA would have would be considered very desirable.

I also hear that there is a tremendous amount unknown about things, but similarly there's a tremendous amount known. In that context, I have to say -- and I also heard, too, and I'm sure Mr. Bracco has sort of alluded to this, there's -- clearly, the Panel has picked up very quickly, or else they knew it beforehand, that PMA is looked upon, in some respects, as a very high burden or challenge to industry that would immediately dissuade getting an FDA test out there. And, in fact, people want an FDA test out there.

We could take this information home because to some extent -- and I really regret this -- in that situation, the EAP sometimes is a very, very valuable tool because one is, as Dr. Whitaker said this morning, the analytical aspects between a 510(k) and a PMA aren't different, so it's not a save on that side. In the terms of demonstrating clinical evidence, what I've heard is people are using it, and there is evidence there, but it's not particularly great evidence. And if there were an FDA-cleared assay out there, it would be terrific to have additional evidence against that assay.

And that almost is a situation for EAP. We can take off on the front end a lot of the expenses, yet getting it in the back end and then having the flexibility that perhaps we're not locked into those specific special controls and perhaps evolve to that state.

And I just want to throw that out, but what I'm hearing, to me, steers me towards an EAP possibility. But again, what people have said, we've heard loud and clear.

DR. ISON: So my only fear with an expanded access program is if you are worried that, about gaps for BK, I don't think that's going to get you what you need because what you would need is correlation with clinical disease, which would be biopsies and whatnot. You're not -- if it's expanded access, you're done. The biopsy's been done. You're basically following patients. I don't think you're going to get a lot of the utility --

DR. GITTERMAN: And I have to apologize. That's my fault. This is expedited access, which is very different from a variety of drug access. The idea under expedited access is

that between ourselves and the community, and of course, the sponsor, we would establish when the assay is out there, because they could now market it. There would become collection of data which would perhaps answer any significant clinical question, if it's at all possible.

DR. ISON: Again, respectfully, I'll say that I think that that's farfetched. I think that unless it's part of a clinical study, getting the fully robust data that you would need to fill the gaps that I think we've highlighted, to kind of hope you're getting it by chance from picking and choosing, not going to happen.

DR. GITTERMAN: Boy, this is interesting. Again, I hate, you know, sort of doing this, but I think Dr. Pereira had mentioned having a claim for monitoring. Correct? Didn't -- during your talk, you mentioned wouldn't it be nice to have a claim for the BK device of monitoring therapy in response to therapy?

DR. PEREIRA: Potentially, in the future, that's right.

DR. GITTERMAN: And didn't you mention brincidofovir, which I know I'm mispronouncing, as a possible therapy out there?

DR. PEREIRA: Yes. So there --

DR. GITTERMAN: Or was that the EBV discussion?

DR. PEREIRA: There are emerging drugs that have activity against --

DR. GITTERMAN: Right.

DR. PEREIRA: -- BK.

DR. GITTERMAN: Certainly, one could suggest, and I -- you know, if there is an FDA regulatory action and assay, we would certainly encourage sponsors to use it in drug trials, in fact. That would overwhelmingly be their preference, from the drug side. And we could make, under the expedited access pathway, that you provide the data from the study, you validate the clinical benefit, and this is something we can include in the label. And if

everybody is comfortable at that point, conceivably it could go to a PMA status.

There's -- we're very clever. Believe me.

DR. ISON: Although it's clever, you're still doing a clinical study.

DR. GITTERMAN: Oh, absolutely.

DR. ISON: You know, so again, I think that --

DR. GITTERMAN: Absolutely.

DR. ISON: -- we just need to be upfront that whether you're kind of tacking it on through some regulatory process to a clinical study, unless you have a prospective clinical study, you're not going to fill in the gaps.

DR. GITTERMAN: Oh, we are not in disagreement. It's the idea that, again, hooking onto an ongoing clinical study is the best way, in a lot of ways, to get that information. And I don't know there'd be any denying around the room that we'd all feel very comfortable if we had really -- for the assay that we're recommending that has the FDA imprimatur, that we have some strong clinical evidence that say -- and this is, to be honest with you, exactly what happened with CMV.

As it evolved, there was the VICTOR study. And when FDA took the output, that was just the very, the very fortuitous circumstance where the drug manufacturer happened to be the device manufacturer.

From what you're saying, I think is absolutely true. It would be beyond the resources of any device manufacturer for -- in the grand scheme of things, it's not a large, you know, it's not a large use, as important as it is to support that. But that EAP program would give us that hook to say, yes, we could all negotiate, so there is a revenue stream at the time, and everybody has the confidence, at least analytically, all these things were well done, yet -- and also they sort of do that. Yes, we have something, because otherwise, if this goes in through de novo, every other assay that comes out there may not be any better, and we

may never have good evidence.

But your points are very well taken. And I -- please, bringing them up is excellent.

DR. SCHAENMAN: Joanna Schaenman here.

I want to say that I do agree with Dr. Pereira that brincidofovir seems promising; however, I think the current forecast for that drug is very cloudy and uncertain right now. And I think that trying to bring BK along with that drug is going to delay things unnecessarily. Maybe I would have felt differently 2 years ago, but right now, I wouldn't pin this need for BK better diagnostics to brincidofovir. I think we'll wait and wait.

Again, I really think this is a clinical need that's urgent, and we shouldn't have a pathway to an FDA-approved product that's going to be slow.

DR. GITTERMAN: Oh, again, and I -- really, please, I will be properly chastised, but other people will learn from my mistakes, that an EAP pathway doesn't necessarily have to be slow at all. You would -- again, I'm not trying to push you to what I believe, just to inform the Committee that we could -- that pathway would not be any slower for a sponsor. What would be different is that they would have the obligation to collect that data whenever it became available. We could all agree that this is a way to answer a significant clinical question, so there's a clear intent, indications for use.

DR. SCHAENMAN: I don't disagree. I just can't foresee how that is going to happen in the future, for BK, unfortunately.

DR. GREEN: So Mike Green.

So I think the issue here is that I agree with Joanna that I think that right now, brincidofovir is struggling to prove its efficacy for any clinical virus at this time. And having said that, the clinical evaluation is following a patient in whom the treatment is reducing a drug rather than adding one, which tends to mean that there's not going to be a pharmaceutical company that's going to offer the money, which really then brings it back

down to the sponsor developing this device.

And so I just don't know how expensive and how you do that. One way they do it is they sort of ask the clinical sites to do it for very little money. And then the clinical sites start to lose money actually doing these studies because they have to invest their time and energy. And so the clinical sites say no, and so you're left with no clinical data that are generated. Despite an understanding as good citizens, and wanting to take care of our patients, our institutions sort of frown a lot on us losing money on these research studies and don't give us approval to do them.

DR. BEAVIS: Yeah. This is Kathleen Beavis.

And also I want to reiterate something that Dr. Schaenman said a little bit earlier, which is given what we don't know about BK, I'm still not convinced that it meets the, you know, high level for a Category III in terms of life-sustaining or life-supporting use and the other criteria that are there listed.

DR. ISON: Although again, my thinking is that we were given a flow diagram. It doesn't go from the bottom up. It goes from the top down. And so although you could be, you know, impacting life or sustenance of life or function, if you can come up with appropriate measures to kind of mitigate against that, then that would allow it to be Class II.

And I think there is -- although there are gaps, there is a massive amount of data on BK virus. And I think one of the reassuring things that was presented by Dr. Cook, and has been presented by several investigators is, although we didn't have an international standard, we didn't have all these things, there's a lot of linearity with the assay when you compare multiple --

So, you know, some of the challenges that we even have today with the CMV assay, we may not have to the same extent with this. And so I think, you know, there is published

guidelines from several groups, with thresholds on, you know, what to consider. I think, as we heard from Ajit, people are treating based on a viral load with confidence, and not doing a biopsy, which also, by the way, probably is far more risky to the patient than the viral load.

And so again, I think that kind of the totality of the information really speaks to this being -- although it's regulatorily just starting, is actually pretty far down the line.

DR. PETTI: We have this esteemed Panel of experts, and I would just like to ask both Dr. Flatau and Mr. Simon, are there any particular questions that you have of us that perhaps would help you?

DR. FLATAU: So, I mean, in my mind, I really don't know whether it should be a Class II or a Class III, the BK virus. I think all of these tests, I think, we would like. I certainly, as a patient, would like to have a test done, and it says yes or no. And these apparently say maybe, very often. And that -- you know, that's the problem. It seems like the same patient who got the same test at the same lab, two different clinicians would decide different things.

And so I think that the important thing is that there's standardization on -- I mean, work towards standardization on these tests so that different tests can be compared to each other, you know, internationally, nationally, between centers. And whichever pathway makes that happen faster and more easily is the better way to go.

MR. SIMON: Basically, just to add to that, it appears to me that, from a patient standpoint, if you have an assay that is classified by the FDA, whether it's II or III, it has more oomph, it has more prestige, it has more backing than one that doesn't. That's --

DR. BADEN: So you -- the VICTOR study established the CMV assay. That, in part, was aligned because a particular sponsor had a particular need, and all the forces were aligned. What speaks very loudly to me is the absence of any other diagnostic in this space

moving forward. And it's hard to think Sponsor A is going to want to do charity for Sponsor B, so unless you happen to have that alignment.

And then as has already been mentioned, these tests are being used not only for these viruses, but a slew of other viruses, because we're trying to manage patients, and technologies emerge that may help us.

So I think you have to do what you're doing, which is figure more creative ways to generate data that can be clinically -- that can clinically guide, because I'm not optimistic that Class III studies are likely to be done unless you have another alignment.

So I think the issue with brincidofovir or any other Compound X -- if Compound X emerges that has real activity, then the company may invest in the surrogate. But that has to do with alignment of self-interest, rather than for free or coming out of our hide, we develop something for public good that we're then punished because we're not productive elsewhere.

DR. PEREIRA: Maybe to address that issue, perhaps could there be a stipulation -- or I mean, clearly, postmarket studies would be -- if there is a de novo Class II classification, could you perhaps create or we can craft postmarketing studies to that effect, should there -- a drug that comes up in the future that's effective?

DR. GITTERMAN: We'd have to -- it's a very interesting question, because you can, even under de novo, specify certain studies that might need to be done. There's more flexibility than not. But this particular case, we'd have to talk to our counsel, because sometimes if it's in a special control, you're sort of implying everybody has to do it.

So your point is well taken, and we could go back with it. I think the tone of the Committee, of what people are trying to say is very, you know, is certainly very clear to us. But that's a very good point. This is something I'd want to discuss with counsel.

DR. PEREIRA: The question that I have is could there be a stipulation -- and maybe

this is completely unrealistic, of establishing internationally recognized standard before anyone can apply for a de novo Class II? I think, clearly a lot of the discomfort here is that there's no standard, or the standard that there is, is pretty bad. So could there be a stipulation for that?

DR. GITTERMAN: Well, it's very difficult in the de novo setting to do that. In the PMA setting, of course, one could do it. That would have been the case had there not been a -- it would be very complex. And again, anything is on the table. And any sponsor who came in with a pre-submission, we would listen. I mean, anybody who could put in a package to say this is how we would demonstrate that a drug is safe and effective for the intended use, and in fact, you know, would have special controls that would establish the benefit and risks are addressed, we would listen.

Our complete goal is really to help the public, and the last thing we want to do is hold things up. So the fact is we would listen. And that would -- to me, I'm sure the companies listen as much to what the Committee says, but still, even in the PMA or the 510(k) world, it's going to be a large burden on the companies to put that forward. But what you're saying is not off the table, but to give you perhaps a correct answer, I would have to go to counsel.

If I could just answer one question. Earlier, people kept talking about a commercial assay as a comparator. Did --

DR. BLUMBERG: Not as a comparator. I think just that there's a commercial assay that is commonly used.

DR. GITTERMAN: Yeah.

DR. BLUMBERG: So not a -- but I mean, I don't really know enough about the performance characteristics of this assay, which is so commonly used, especially now after this presentation where I've learned a lot more about the virus than I actually realized. And

so I'm not really sure of the performance of that commercial assay. It's just that there is one that's out there, that has been heavily marketed in the transplant world, and I think frequently used.

In fact, they were like offering it at one point essentially for almost free, to try to get people to -- you know, they were like offering a lot of different scenarios for it so that I think -- that it's just something that's -- people don't realize the whole process of certification to know that there are actually issues beyond that which, you know, may be just some clinical correlation with this particular assay. That's my sense, at least. I don't know.

DR. PETTI: I mean --

DR. GITTERMAN: I will just say the point is, of course, that a commercial assay is an LDT.

DR. PETTI: Dr. Hayden. Do you have a comment?

DR. HAYDEN: I mean, I think there are commercial reagents, but no commercial assays per se. And as soon as -- so there analyte-specific reagents, and there are probably a couple of them that have a fair market share. But that represents actually a huge number of actual assay designs. And so you can't really point to that and say this is an assay.

DR. GREEN: I think what they're referring to is that there is a laboratory, a commercial laboratory that provides this test the same way that Quest provides a variety of different tests.

DR. HAYDEN: So a reference laboratory setting.

(Simultaneous speech.)

DR. GREEN: Right.

MR. BRACCO: You can't go through de novo if there's a commercial assay out there because that would become the predicate.

DR. GITTERMAN: My point is commercial -- I mean, in this case, if it doesn't have FDA approval or clearance; it's an LDT. I mean, commercial, in this setting, means an assay that's being promoted but, in fact, does not have FDA approval. It essentially is looked at as an LDT, which is what it is, yes.

MR. BRACCO: I also -- oh, I'm sorry.

DR. GITTERMAN: No. And also, too, I'm not quite sure, and somebody could help me, what makes a reference laboratory, other than somebody saying we're a reference laboratory. Can --

DR. ISON: It's a commercial laboratory.

DR. GITTERMAN: Yeah. So, I'm sorry. Please.

MR. BRACCO: I just want to -- something piqued my interest. Someone brought up the fact that they weren't aware if there was an assay or not available by a manufacturer. And FDA -- and I'm really asking this of you, FDA never petitions the community as to whether or not a de novo should be used, a de novo pathway should be used for a particular test or device, unless there is a manufacturer that has already asked that question, correct?

DR. GITTERMAN: No. And it's a really good question. We are trying to do the right thing and trying to engage. And the fact is, as people commonly said, people are scared to sometimes talk to us, if they're making the decisions between whether to invest in one or not. Sometimes having the guidance to say maybe we won't need a PMA, maybe we will EAP, what are the options? So in a sense, trying to be proactive and hearing the community say, you know, how much we want it or need it, etc., may serve a purpose.

So your point is correct. It's not common at all. But this has been asked, and I hate to bring up the previous draft guidance because I've asked us to consider that out of scope. But there are -- have been some concerns expressed. And I think the IDSA, in fact,

expressed that, that if certain proposed or thought balloon proposals were to enact, that might pose certain risks for things. I don't think that should be a consideration, and I'm very, very glad that has not come up.

But I think that has pushed some of the community to think it was an issue. And I think, again, we're very appreciable. We're just trying to do the right thing.

DR. ISON: So one thing, and Randy or Dr. Cook may want to talk about this is, I think we've impugned negatively the WHO standard for BK. I think that there are clearly, as you identified, some challenges, but this went through a relatively rigorous process to become a standard. And, you know, I'd be interested in your thoughts. Do you think it's weak? Do you think that there are significant problems that would prohibit its use as a standard for companies to --

DR. HAYDEN: I think it's got significant flaws. I think -- personally, I think that there are potentially special controls that could be designed, where a company could demonstrate that they have mitigated risks from those flaws, although I think that, over time, it needs to be revised and address those flaws. But clearly, you know, it depends on which genetic target you look at. It's not the same thing as a NIST standard, and it never will be, because who does biological controls and does it by consensus? But they, in turn, as Linda has said, could mitigate their risk by actually sequencing things before they put them out.

But I mean, I think that -- yeah, it's certainly flawed. It's not irreparable, but it needs -- and, you know, it could be used, with a lot more effort, to address the known deficiencies, I think.

DR. COOK: Also, I would just say, I was at the NIST meeting in June and sort of presented this data and showed it to them, and they were pretty horrified. Horrified is maybe not the right word, surprised. And they, I think, are in the middle of trying to

confirm our data.

So I asked them, as I left, what they were going to do about it. And obviously it's a tremendous bureaucracy, so it's not entirely clear whether they're going to pull it off the market or try to sort of mitigate what's going on. One could imagine that one could just change the number, depending on which primer set you're using. If we could all sort of agree that the coverage is really the issue and -- you know, because what I just showed you is a couple of primer sets, which may or may not hold up for all the other primer sets.

The NIST material that I showed you is actually not a standard. It was just something that they were in the middle of playing around with. It's small enough virus that you can actually clone it. And so what was talked about before, it's probably entirely possible that that might be the better way to make this particular material because you really can't culture it very well without making a lot of deletions.

So the NIST material is kind of available, but when I was talking to them yesterday actually at the AMP meeting, they basically said they'd kind of put it on the back burner while they were doing other NGS things. So I think something that came out of this Committee that said we absolutely need somebody to do something about this fast might go somewhere.

And then just to back up and clarify, there are approximately, internationally, I think, five or six assays for BK on the market. There are -- the international market, I should say. There are CEU-marked assays that are the whole entire assay all together, the extraction, the PCR. What's available in the United States are the ASR versions of two of those. And as Randy said, that just means that they can sell you the reagent. They can't tell you anything about it. They can't tell you where it is. They can't tell you any performance. And so you have to do all that yourself.

So they're not really assays. They're both marked as ASRs. And to my knowledge,

they're both just single primer sets.

DR. PETTI: Thank you, Dr. Cook. That was very informative.

So, Dr. Gitterman, it appears that we have had varying opinions about the classification of BK virus. While we did not necessarily specifically address special controls per se, perhaps you gleaned enough from our conversations on what those controls might look like?

DR. GITTERMAN: Absolutely. And this was very valuable. And I completely agree with where you're going because the clock's ticking.

DR. PETTI: Yes. And we'd like to segue to EBV. And let's have Dr. Green kick that one off.

DR. GREEN: Thank you. Mike Green.

I'm willing to wager, with high stakes, much better than I would have on polling results, that I've seen more EBV loads than anybody else in this room, and that may include the laboratorians, although that may not be the case.

Dr. Gitterman called BKV the Wild West. If that's the case, then EBV loads will probably be the Wild West to the fourth log.

I think issues that we probably need to understand is what is the goal of the measurement you're doing? Are you trying to diagnose disease in a patient who has a clinically compatible illness? Are you trying to follow resolution of disease or response to therapy?

And I will put a caveat that persistent high loads may definitely be seen in patients who recover from PTLD. Those loads may persist for months, if not years, without progression to recurrent disease, although the absence of that persistence probably means you're at much -- you're at a lower risk, and depending on the type of the transplant and what you do in response to those loads, may mitigate that risk.

And then, of course, are you using the assay as a strategy to prevent the development of EBV disease and PTLD, or PTLD? And again, I want to clarify that in my mind, we are doing a disservice to our patient population to only say PTLD, which is a histologic condition where you have effacement and destruction of tissue that makes it sort of moving along a cascade, as opposed to something like EBV hepatitis or EBV enteritis.

And I think that which compartment you measure would probably want to take into consideration what goal you're doing. It's possible that you could measure one compartment to achieve all those goals, but the performance of the assay, in terms of sensitivity and specificity, would probably calculate differently depending upon the assay that you did.

So if you did whole blood, and you were trying to preempt patients, you would probably have better sensitivity, perhaps you'd have less specificity. If you did it for disease, you would have still very, very, very good sensitivity actually, but your specificity would probably be lacking. And if you did plasma, you'd enhance specificity, but you would definitely lose sensitivity. And there are cases like that, that are published in the literature. And so it really comes down to what your goal is.

There is an international standard. I don't think that people have found so much problem with the international standard, but my understanding is that many labs were busy implementing CMV. And so at least in our experience, and at least in several other labs that I'm aware about that don't -- only now more recently introduced the EBV standard. But we saw, on the data that were presented, that there was some tightening of the spread when they did that.

And, of course, there is no pre-existing comparator assay that is either Class II or Class III FDA cleared or approved, although there are assays that have been in clinical use for in excess of decades if -- in excess of a decade, if not longer.

I do think that there's a tremendous need for this, and this is particularly true in the pediatric population because my colleagues that take care of adults see only about 5% of their patients who are really at real risk for a primary infection, and for at least organ transplant patients or solid organ transplant patients, it's primary infection where the disease is really going to manifest.

So, in kids, we see this a lot, particularly those organs that we do in younger children, where they're really too young to have had primary EBV disease, and particularly those that get adult donors, which happens with some frequency, because their donor's going to be positive, the recipient's going to be negative, and they're at risk for primary infection.

So there is a difference in pediatric versus adult, although if you're adult who has primary EBV infection, I suspect, after organ transplant, that your risk is not so different than a kid who has the same organ, and in general, that means a similar exposure to immunosuppression. It's very dependent upon your immunosuppression exposure. The less you get, the less your risk is, and in fact, the primary response to this, if you can, is to reduce immune suppression.

Antiviral therapies have not been demonstrated in a clear fashion to have any impact, although they're frequently used. So the ganciclovir, acyclovir, really for those that don't know in the audience, and our sort of other members of the Panel who don't do this for a living, you can actually inhibit this virus from making copies of itself and busting out of itself in the test tube or in your saliva. But in the body, there's a proliferation of cells that had been immortalized by the virus, transformed by the virus and told to proliferate.

And they do this using human enzymes. And the antiviral medicines we use don't inhibit the human enzymes, because if they did, they would be cancer agents, and they would be toxic.

So, a lot of that said, I think there is a need -- when my patients leave my hospital, they go home, and their insurance companies may mandate that they get a specimen from Quest. Quest not only doesn't actually stipulate, but if you call, you'll find out it's plasma, and I like whole blood, so there's a major difference there. Two, if you ask Quest, tell me what your assay means, give me some idea of any kind of idea of what a high load is on your assay, they can't tell you because they have no clinical correlation whatsoever.

At least with my assay, I can tell you a great deal about our clinical correlation based on a long-term observation. And, in fact, we transitioned from a PBL assay to a whole blood assay, and we did the correlations between those two. So we have both 10 years of correlation experience, or 12 years with our new assay, and that was informed by about 5 or 10 years of our previous assay.

So I would like us to have an assay. I would be fine with us to say a Class III, but I do wonder if there's a Class III, if it's such a barrier, that we will not get that clinical assay, and we'll be left in where we're at.

I will just tell you that right now, the Children's Hospital Pittsburgh is doing liver transplant with the University of Virginia. And they were doing an assay that was serum-based, completely discordant from our whole blood assay. And we've now told them, thank you, just send us the blood, we'll do it at our assay so we can at least interpret it, and -- while we're looking at it there.

So I would love to see FDA have a pathway to acceptance. Maybe it's only Class III, but then I suspect you'll never get it done. I don't know how to get Class II done.

DR. BADEN: So Mike gave the short version.

(Laughter.)

DR. BADEN: So my answer is the same as the previous, not Mike's, but my previous answer for BK. I think it depends. I think I can see a path to a de novo Class II, but it'll

depend on the specific issues. And Mike has raised many of them. There are target issues. There are latent versus lytic. There's asymptomatic shedding. There's syndrome. There's host. There are kinetics of risk. And so there are potentially intervention issues, immunosuppression issues.

So I think all of these are the kinds of issues that have to be weighed. They're manageable, mitigatable, frameable, but it all depends on the assay and what is trying to be achieved. So I think that the -- depending on the question put to the FDA, would influence whether or not a path to a de novo Class II is possible, or the EAP. The need for standardizing and harmonizing these kinds of assays, I think, is tremendous, and that's what we've been discussing.

And so figuring out how to find a clever pathway to allow a more standard development, I think, is critical, because what is going on right now is we're getting these assays and a dozen more on different viruses, and we're all interpreting them to the best of our ability, but with limited guidance or data.

DR. CHOU: I think, with the number of uncertainties, to me, it's very difficult to classify this into the de novo pathway.

DR. LA HOZ: There are certainly a fair amount of uncertainties, but also -- I don't know if this of value, but I see mainly adults, and the disease is not as frequent as in children, mainly in thoracic organ transplants compared to some others. Even though our center does a fair amount of thoracic transplants, the percentage is low. And I wonder if the higher complexity, given the rarity of the disease, is going to be a barrier to some of the regulatory issues, if it was to be classified as III.

DR. MEYER: I don't have too much to add. I just think it does have a need, if there would be a way to figure a pathway that -- I think that Class III would be difficult for anyone to pick that up.

DR. BEAVIS: I agree. And I'd like to say that this assay presents particular challenges for the laboratories. We tried to switch to plasma. We had difficulties with that and, you know, we're back to whole blood.

But one of the challenges with whole blood is that, for regulatory purposes, you have to use controls of the same matrix as your test. And it is -- you know, we got caught by one of our inspectors on an accreditation thing, and nobody else knows a way around it. But so it presents special challenges for the laboratory. I'd love to see a test available for this.

DR. ISON: So I think that the level of unknowns still are a bit -- are the part that is still troubling. I think that you have a breadth of indications. You know, we've been talking mostly about PTLD, but I think that there are a number of other potential indications that they could go after. And again, I'm going to go back to what's the lower limit of detection that we need to be able to detect reliably to not miss a factor.

Now, granted, I understand it's going to be very high, and it's going to be trending upward. But --

(Off microphone remarks.)

DR. GREEN: I just want to intercede here because I think there are very strong data in the literature that low levels of EBV, unless they become high levels of EBV, on whatever your assay calls low and high, don't really connote risk. And so I'm not so sure that understanding the breakpoint for less than 200 versus -- that has any meaning at all. I don't get concerned at all, other than to recognize, aha, primary infection.

If someone's previously been positive and they have a low level -- and again, depending on what you call, in your assay, a low level, and particularly I'm dealing whole blood here, not necessarily talking about plasma, I don't think that it's particularly important.

DR. ISON: Yeah. I think, though, I would still come back to, if there's a lot of vagary from center to center, about what that low level is, then figuring out what the -- it just -- there's, I think, too many questions. And the sequelae, so if you are wrong, you have unabated disease potentially, although again, I understand, you're going to be doing serial testing. I don't think it's ready for Class II.

DR. SCHAENMAN: Joanna Schaenman.

I think this is a very clear contrast to BK where, again, in my opinion, we've got a real preponderance of evidence, we've got clear guidelines, and we know that following the guidelines impacts patients' clinical outcomes.

I just bring that up again to say, for EBV, I don't think we have answers to any of those questions. We don't know how to use the test. We don't know what part of the blood to test, and especially in adults, as Dr. La Hoz mentioned, it's kind of so rare that we test relatively frequently, but basically, if it's positive, we frequently ignore the result. And if we think someone has PTLD, regardless of their EBV viral load, we'll pursue that diagnosis. So it just adds to the confusion.

I think that Dr. Baden's comment of "It depends" is maybe one of the most helpful comments here. And I think that because I think we're all anxious to see a way for getting an FDA-approved test, perhaps it would make sense to come back with a specific indication and question, clinical question, because then we can better define what is it that we're looking for in terms of special controls.

DR. WELCH: David Welch.

After hearing the presentations and the discussion up to this point, and trying to channel my own experience into this, I'm not sure. I'm a little on the fence. But I think, based on my own experience, in which it's used primarily by pediatricians and, I mean, I don't know if there would be an indication for pediatrics only or anything like that would be

appropriate, but I would say I would lean toward going forward with a recommendation to it be considered in a de novo format.

DR. PEREIRA: I think, based on the risks, Class III makes more sense.

DR. HAYDEN: Randy Hayden.

It is interesting, the contrast with BK, right. I mean, I think that it's almost the inverse, and that we -- I think the technical challenges to assay design are still present but perhaps less, and the path towards a WHO standard that is functional seems a little bit shorter, although the data are still early. And I do agree, perhaps with a narrower question and a very specific indication, one could find a de novo path. But that would sort of depend on the indication.

But given the number of centers doing this testing, it does beg the question as to whether, you know, there is some area of agreement on and some preponderance of data for at least a narrow indication. However, you know, across the board, it would be hard to make that case.

DR. BLUMBERG: I think this is a really challenging area, and I think, for all of the reasons that people have noted, there's clearly a disconnect between the adult and the pediatric experience. There's clearly a lot that we don't know about viremia, based on just even different assays, whole blood, plasma, serum. But we also know, based on some unpublished data, that normal people can be BK -- I mean, EBV viremic for a very long period of time without clear, defined clinical associations that we know of yet.

And I think there is a potential for harm, because since we don't really know what to do with the information, and there's some anecdotal data giving things like rituximab to people with persistent EBV viremia, there is this question of if we give this information to people, what will they do with it?

And so, I think, while I could see a very narrow indication for going with Class II, that

if we're looking broadly, I don't think the information is there yet to go Class II, and I would probably say Class III. I could see that that could change, depending on a study design, but right now III, I think.

DR. KOTTON: I think, similar to the last two, I would agree with a Class II de novo, although I definitely struggled with this. I share on the sentiments of many people in the room. I do see patients -- it is, it definitely still is the Wild West. That, I definitely concur. I see patients who have mismatched situations, who have EBV viremia and go on and get horrible lymphomas, and some of them die.

And that happens once or twice a year. And, you know, I don't like that I am sending an assay -- and I actually, personally, in my program we try to do screening on any mismatched situation; whether it's evidence based or not, you know, remains. But we've had some horrible outcomes, so that's why we do it.

And I guess I would really just like to know that I'm using a more regulated assay with some better support than what I'm doing now. So I'm sort of -- I think the reason my -- I feel some conflict of personal interest, as a physician, just taking care of my patients, that I really would like a Class II because I don't see anything happening if it's a III, so --

MR. SIMON: Tom Simon.

Again, qualifier, I am not qualified. But from the standpoint --

(Laughter.)

MR. SIMON: But from the standpoint, if an FDA test is going to make the test more, with more oomph, with more qualifiers, with more -- with less risk, more safety, and I definitely think it should have some designation. Which designation is up to the experts.

DR. FLATAU: Art Flatau.

So my feeling, in terms of -- particularly in terms of stem cell transplant, there's -- the risk in T-cell depleted transplant is there's probably over 5% mortality from PTLD in

those patients. And there does seem to be some increase in the number of T-cell depleted transplants that are being done. Actually, the last time I was here, 3 or 4 years ago, was for a device to do T-cell depletion; that was approved, and there's a lot more haploidentical transplants being done which are all T-cell depleted.

And so, I think that there -- again, I don't know what class it should be in, but there is a definite need for being able to test for EBV and probably, as well, a need for effective treatments for EBV because PTLD in stem cell transplants is a very ugly situation.

MR. BRACCO: I just want to satiate some of your concerns regarding the fact that the assay won't be developed or may not be developed because of the fact that a clinical trial is needed. That is true somewhat when you have a small little company, a startup, and they have to run a clinical trial. They might not want to do that. But for a larger company, the fact that a clinical trial has to be run, or a PMA, you know, is needed for the approval, they usually won't shy away from that.

They will shy away from lack of prevalence, obviously, and we have mechanisms for that, humanitarian device exemptions. But I don't think you should let that influence you because if there is a need, then the big companies will do whatever they have to do to satisfy that need.

DR. PETTI: Thank you. Any further comments?

Dr. Gitterman, was this an adequate discussion?

DR. GITTERMAN: It was. And I have to say, it's exceptionally valuable because again -- and I feel somewhat culpable for this, but I think we've heard that the challenges have been well expressed. And I think people really expressed how clear this community -- having at least the analytical components of an FDA-cleared assay is, I think Dr. Hayden said, or Dr. -- or Simon said, imprimatur.

And I think there's a big challenge to us, no matter what the regulatory standard is,

III or II, whatever is, how we can work together with sponsors to overcome these challenges and come up with a model that gets some of the things I heard around the table addressed, while similarly making the situation better than it is now, by at least having assays which have certain qualities that are with far greater transparencies. And I think this is really invaluable. And again, I can't appreciate people more.

It's just sort of a -- one thing for the people who are only here today, you can thank goodness you don't have to be here tomorrow. That' another challenge. For the people who are here tomorrow, I give especially -- you know, special thanks for your masochism. But really, this is extremely valuable.

I also want to make one point, too, is we realize it's a lot of paperwork. It's a difficult process. But for the future, as other questions arise, it is very, very valuable. For regulatory questions, we do have to do those publicly. They have to be done transparently. But for technical questions and specific questions, it gives us a much clearer path by which we can ask your opinion in a formal way. So by doing this, you really have done a great service for us, and we -- honestly, speaking for the Division and the FDA, we can't thank you enough because this is quite a sacrifice, and we really, we genuinely appreciate it.

DR. GREEN: I want to make one last comment about EBV, and I'm the one that said it was Wild West at the number III. If you had conveyed this Panel with only pediatric transplant infectious disease people who deal with children who are EBV mismatched all the time, you would find a lot -- we would still have some of the issues we talked about, but you would find a lot less uncertainty and discomfort about how to react to these tests.

I often tell people that I think of this EBV quantitative load as a semi-quantitative test. And as soon as you said it's semi-quantitative, some of the barriers are different. But I interpret this as a semi-quantitative test, and I think about it in the different circumstances that I described, and I do it with some comfort in understanding some of its limitations but

also really understanding both its -- I think, pretty well, its performance.

And so I do want FDA to understand that because we've chosen a bunch of adult transplant ID experts, their feeling about looking at this test, because I'd recommend against doing this test in seropositives unless they have clinical disease that makes you worried that you have PTLD.

But I use it all the time in seronegatives who don't have disease and who I monitor subclinically and then maybe progress to disease. And I think a lot of my colleagues who take care of children would feel the same way. And so there is a differential experience here, just as I don't deal that much with BK and they deal with it all the time. So just keep that in mind as you think about paths forward, because it's really -- this is really a pediatric problem. Thanks.

DR. GITTERMAN: I would like to make the comment; we have addressed that concern by hiring one of Dr. Green's fellows, so -- which is --

(Laughter.)

(Off microphone remarks.)

DR. GITTERMAN: She was a medical student, my God. But he did such a good job, and --

DR. KOTTON: Camille Kotton.

Mike, I just want to counter that by saying I actually feel the same way, maybe because, in part, you trained me, but I actually feel very comfortable with these assays in adults as well. So I didn't say that before.

DR. PETTI: How many others --

DR. BADEN: And we do see disease in adults.

DR. KOTTON: Yeah, we see plenty of disease. So -- yeah.

DR. GITTERMAN: Before we close, can I just -- I thank the Committee, and I would

just like to thank my colleagues, because again, I'm a physician, and there are people really who have world class expertise. And I, you know, again, doubt that I could name everybody there. So I won't waste everybody, but it would be obviously impossible to understate their contribution on a daily basis to solving difficult problems in the midst of a Zika epidemic.

DR. PETTI: And many thanks to the Panel. Your expertise is really astonishing, and great public service that you did today. A special thank you to our Patient and Consumer Representatives. It helps us, at least from my perspective, really be better doctors. That perspective is invaluable. And Industry, of course, thank you for saying that Class III designation would not be prohibitive for us who have tools at our disposal to improve patient care.

Again, thanks to our guest speakers, Dr. Linda Cook and Ajit Limaye. Members of the public, thank you for your comments, and certainly the FDA for all your hard work.

Dr. Gitterman, any last comments?

(Off microphone remarks.)

(Laughter.)

DR. PETTI: Wonderful. I now pronounce the second session of the November 9th Panel meeting adjourned.

(Whereupon, at 4:56 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:

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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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