UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

MICROBIOLOGY DEVICES PANEL

+ + +

August 16, 2016
8:00 a.m.

Food and Drug Administration - White Oak Campus
Building 31 - The Great Room, Room 1503
Silver Spring, Maryland

PANEL MEMBERS:

ANGELA M. CALIENDO, M.D., Ph.D.	Panel Chair
KATHLEEN G. BEAVIS, M.D.	Non-Voting Member
KIMBERLY E. HANSON, M.D., M.H.S.	Non-Voting Member
CATHY A. PETTI, M.D.	Non-Voting Member
KENNETH H. RAND, M.D.	Temporary Non-Voting Member
PETER WOLFF	Temporary Non-Voting Member
LIZZIE J. HARRELL, Ph.D., D(ABMM)	Temporary Non-Voting Member
MARK G. MARTENS, M.D.	Temporary Non-Voting Member
LORI E. DODD, Ph.D.	Temporary Non-Voting Member
KELLY J. HENRICKSON, M.D.	Temporary Non-Voting Member
MARGARET R. HAMMERSCHLAG, M.D.	Temporary Non-Voting Member
FREDERICK S. NOLTE, Ph.D., D(ABMM), F(AAM)	Temporary Non-Voting Member
MAUREEN BEANAN, Ph.D.	Temporary Non-Voting Member
CHARLOTTE A. GAYDOS, Dr.P.H.	Temporary Non-Voting Member
BARBARA VAN DER POL, Ph.D., M.P.H.	Temporary Non-Voting Member
DAVID R. KIMES	Industry Representative
THOMAS G. SIMON	Consumer Representative
NATALIE COMPAGNI PORTIS, Psy.D., MFT	Patient Representative
SHANIKA CRAIG, M.B.A.	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

ALBERTO GUTIERREZ, Ph.D.
Director, Office of In Vitro Diagnostics and Radiological Health

UWE SCHERF, M.Sc., Ph.D.
Director, Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health

STEVEN GITTERMAN, M.D., Ph.D.
Deputy Director, Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health

TAMARA V. FELDBLYUM, Ph.D.
Chief, Viral Respiratory and HPV Branch
Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health

TARA GOODIN
Press Contact

FDA PRESENTERS:

GINA CONENELLO, Ph.D.
Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health

INVITED SPEAKERS:

GAIL BOLAN, M.D.
Director, Division of STD Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
Centers for Disease Control and Prevention (CDC)

STEPHEN LINDSTROM, Ph.D.
Influenza Division
Centers for Disease Control and Prevention (CDC)

OPEN PUBLIC HEARING SPEAKERS:

MICHELE SCHOONMAKER, Ph.D.
Vice President of Government Affairs
Cepheid

CHARLES SAILEY, M.D.
Laboratory Director
Molecular Testing Labs

BALA RAJA, Ph.D.
CEO and Co-Founder
Luminostics

SEAN PARSONS, M.B.B.S.
Founder/Managing Director
Ellume Pty Ltd
East Brisbane, Queensland, Australia

JULIE AKER, B.S., MT(ASCP)
President & CEO
Concentrics Research

INDEX

INDEX

M E E T I N G

(8:15 a.m.)

DR. PETTI: Hi. I would like to call this meeting of the Microbiology Devices Panel to order.

My name is Cathy Petti, and while we're waiting for Dr. Caliendo, we will commence this meeting. I am an infectious diseases physician with expertise in innovative diagnostics and infectious diseases. I'm affiliated with the University of South Florida in Tampa, Florida.

At this meeting, the Panel will discuss and make recommendations regarding the appropriateness of clearing or approving of over-the-counter diagnostic tests for the detection of pathogens causing infectious diseases, focusing on respiratory and sexually transmitted infections. The Committee will evaluate the risks and benefits to individual patients and to public health associated with clearing or approving OTC diagnostic tests for infectious diseases. The Committee will also make recommendations on clinical study design, analytical study design, and acceptable performance criteria applicable to respiratory and STI diagnostic devices.

Before we begin, I would like to 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 begin with FDA staff. Dr. Uwe Scherf.

DR. SCHERF: Yeah, good morning. My name is Uwe Scherf. I'm the Division Director in the Division of Microbiology Devices, and I have been part of this team for the last 12 years.

DR. GITTERMAN: Steve Gitterman, Deputy Director, Division of Microbiology Devices.

DR. MARTENS: Mark Martens, Chairman of OB/GYN and Director of the Division of Women's Infectious Diseases at Jersey Shore University Medical Center and Rutgers School

of Medicine.

DR. HARRELL: Lizzie Harrell. I am a clinical microbiologist, and I am Research Professor Emeritus of Molecular Genetics and Microbiology at Duke University, and I was formerly the Associate Director of Clinical Microbiology there.

DR. HENRICKSON: Kelly Henrickson. I am a pediatric infectious disease doctor and Professor of Pediatrics and Microbiology at the Medical College of Wisconsin and Children's Hospital Wisconsin. My expertise is in pediatric infectious disease; it's in respiratory virology and in molecular diagnostics.

DR. NOLTE: Good morning. My name is Rick Nolte. I am Professor and Vice Chair for Laboratory Medicine at the Medical University of South Carolina in lovely Charleston, South Carolina. Come and see me. I am a medical microbiologist by training, and I've been interested in sort of molecular diagnostics for most of my career.

DR. HAMMERSCHLAG: Maggie Hammerschlag. I'm Professor of Pediatrics and Medicine at the State University of New York Downstate Medical Center in Brooklyn. Yay Mets. And I just recently stepped down as Director of Pediatric Infectious Diseases, but I'm still involved with the fellowship training program. My expertise has been in chlamydial infections, epidemiology, diagnosis, and treatment, specifically also dealing with issues of diagnosis of sexually transmitted infections in children being evaluated for suspected sexual abuse.

MR. WOLFF: Good morning. My name is Peter Wolff. I am a Clinical Project Manager in the Sexually Transmitted Diseases Branch of the NIAID at the NIH. My areas of expertise are clinical trials and sexually transmitted diseases.

MS. CRAIG: My name is Shanika Craig. I'm the Designated Federal Officer for this meeting today.

DR. BEAVIS: Good morning. I'm Kathleen Beavis. I am a pathologist, and I'm at the

University of Chicago as the Director of the Microbiology Laboratories and the Interim Director of all laboratories.

DR. RAND: Ken Rand. I am Professor of Medicine and Pathology at the University of Florida. My training is in clinical infectious diseases, and my real life is running the micro lab at our hospital and in molecular diagnostics.

DR. BEANAN: Good morning. My name is Maureen Beanan. I am a Program Officer at NIH/NIAID, the same institute as Peter. I'm in the Division of Microbiology and Infectious Diseases, and I oversee grants and contracts to support the development of diagnostics for infectious diseases.

DR. GAYDOS: Good morning. I'm Charlotte Gaydos. I am a Professor in Infectious Diseases at Johns Hopkins, a medical microbiologist by training. My area of interest is STIs and respiratory diseases, particularly recently as they relate to point-of-care tests and home collection of samples.

DR. VAN DER POL: My name is Barbara Van Der Pol. I'm at the University of Alabama at Birmingham, in infectious diseases. I'm the Director of the STD Diagnostics Laboratory, and for the last 35 years I've been engaged in clinical trial evaluations for STD diagnostics.

DR. HANSON: Hi, I'm Kim Hanson. I am an Associate Professor of Medicine and Pathology at the University of Utah. I am a practicing adult infectious diseases physician and also the Director of the Clinical Labs and Microbiology at ARUP.

DR. DODD: I'm Lori Dodd. I am a mathematical statistician at NIAID in the Division of Clinical Research in the Biostatistics Research Branch.

MR. SIMON: My name is Tom Simon. I'm the Consumer Representative for the FDA. I'm associated with the Cancer Survivors Network at St. Joseph's Hospital in Atlanta, Georgia, and I'm associated with various nonprofits and charitable organizations.

DR. PORTIS: I'm Natalie Compagni Portis. I'm the Patient Representative today, and also a psychologist working primarily with adults and children and teens around chronic and life-threatening illness.

MR. KIMES: Hi, I'm Dave Kimes, Industry Representative. I work at Abbott Diagnostics. We develop instrument systems and IVDs for the core laboratory and transfusion space.

DR. PETTI: Thank you, everyone.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Shanika Craig, the Designated Federal Officer for the Microbiology Devices Panel, will now make some introductory remarks.

MS. CRAIG: Good morning. I will now read the Conflict of Interest Statement dated August 16th, 2016.

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 (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

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

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

employees and regular Federal employees who have financial conflicts when it is deemed that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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

For today's agenda, the Panel will discuss and make recommendations regarding the appropriateness of clearing or approving of over-the-counter diagnostic tests for the detection of pathogens causing infectious diseases, focusing on respiratory and sexually transmitted infections. The Committee will evaluate the risks and benefits to individual patients and to the public health associated with clearing or approving OTC diagnostic tests for infectious diseases. The Committee will also make recommendations on clinical study design, analytical study design, and acceptable performance criteria applicable to respiratory and STI diagnostic devices.

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

David Kimes is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Abbott Diagnostics, a unit of Abbott Laboratories.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all 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 August 16th, 2016, Ms. Natalie Portis has been appointed to serve as a Temporary Non-Voting Patient Representative. For the record, Ms. Portis serves as a consultant to the Oncologic Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

This appointment was authorized by Dr. Janice M. Soreth, Acting Associate Commissioner for Special Medical Programs, on August 4th, 2016.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firm at issue.

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

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. Their telephone number is (410) 974-0947.

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

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

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that

all reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Artair Mallett at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to say your name every time that you speak.

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

Dr. Caliendo -- I'm sorry, Dr. Petti.

DR. PETTI: Thanks, Ms. Craig, for that very helpful and important information that you shared with us.

We will now hear a brief introduction from Dr. Alberto Gutierrez.

DR. GUTIERREZ: Good morning. I'm Alberto Gutierrez. I'm the Office Director of the Office of In Vitro Diagnostics and Radiological Health.

My talk is really to welcome you to a very hot and humid Washington and to actually thank you for your public service. This is a public service. I would like to apologize for whatever we put you through to get you here. It's never a pleasant journey, but really, for us, this Panel represents an important part of our deliberations as we move forward with doing the job we need to do. We take your advice very seriously, and we really appreciate all the discussion and all the points that you can give us. I don't really have to go through again. I think you'll hear over and over again why you're here today. Really, the discussion is really more based on touching on the issues for the FDA.

So the FDA has a mission that most people know, that is, to protect public health. We do this mostly by reviewing devices, in our case, before they go on the market, or by

controlling them after they're on the market. But there is a second part of our mission that most people don't know, and that is we actually work very hard to promote public health. The meeting today is more in the side of promoting. We are beginning to think about over-the-counter devices that do not exist, and in trying to set the groundwork for the companies, for us, and for patients, for everybody, on what will be needed, we need to have some discussion, some benefit-risk. And how do we go about either defining the risks and mitigating them or defining what will be benefits of when the Agency eventually sits down in front of a premarket submission for such devices, that we actually have thought through how are we going to look at these devices?

Why now? Clearly, over-the-counter devices have been around. They actually have been around before the FDA started regulating over-the-counter devices. Glucose meters were over the counter in 1976, before the Agency took on the job of regulating them. And over the counter has always been a very difficult area for the Agency, in part because it is difficult to assess the benefits and to assess the risks of such devices.

I don't know if any of you read an article that appeared in the *New York Times* the end of July on the first over-the-counter pregnancy test, and it was very interesting to see the kind of things that the regulators were worried about in such tests. We were supposedly worried about who was going to be using this pregnancy test and thought it usually would be young females, and we worried about what that would do. So it is very difficult to predict what risks and what benefits devices like this will have in the public, in large part because we don't really necessarily understand how they're going to be used, who's going to be using them, and what benefits and risks are in that landscape.

The couple of things that are coming together in this area right now that make this an appropriate time for this is (1) there is a large effort, including from the Administration, in figuring out what are we doing with antibiotics and how can we decrease the use of

antibiotics? This has emerged as a national and international priority. There are new ways to communicate. Patients have new ways. We have access to information that we didn't have before, and therefore the way that we do medicine is changing. That has something to do with it. And we're entering a new area of new technologies that are making it easier and more accurate to measure things by people who are not necessarily experts in the laboratory. So based on all those things, we think this is the right moment to begin to think about over-the-counter devices and what we need to take into consideration.

So today we would like to hear some open discussion on the risks and benefits. Again, this is the crucial part for us. We would like to obtain some recommendations regarding approaches that we should be considering, and we would like to hear some discussion of what should be the acceptable performance criteria for such devices.

And again, I do want to thank you for your service and -- sorry. I turn the floor back to Dr. Petti. You moved. I was looking for you over there. I was thinking you were gone.

DR. PETTI: We will now hear a presentation from the FDA. At the conclusion of this presentation, there will be time for questions from the Panel members.

DR. CONENELLO: Good morning, everyone. Thank you for coming. My name is Gina Conenello. I'm the lead reviewer on this project, and I work in the Division of Microbiology Devices.

Okay, today I'm going to be talking to you about over-the-counter diagnostics for the detection of pathogens causing infectious disease. First, we need to define what an over-the-counter test is. These tests we are talking about today are available without a prescription and independent of the healthcare setting. These tests are performed by lay users who self-select that the test is appropriate for their symptoms and/or risk behaviors.

So how does the FDA regulate these tests? Typically, regulations are not written specifically for over-the-counter diagnostic assays. Each assay would be regulated under a

separate analyte-specific regulation. Under that specific analyte regulation, a device can be cleared as either prescription use only or for over-the-counter use. The next slide will discuss the studies that FDA generally looks at to evaluate these diagnostic tests.

This slide presents three different pathways to market for diagnostic assays: first, the assays that are performed in a professional laboratory setting. These are CLIA-certified laboratories with either a moderate or high-complexity classification. For analytes that we will be discussing today, FDA reviews these assays under the 510(k) regulation, stating that each new test must be as good as the predicate device.

For the 510(k) laboratory setting, we normally review analytical studies, such as limit of detection, cross-reactivity, interfering substances, reproducibility, and inclusivity. We also look at a clinical study, and that clinical study uses specimens collected by a healthcare professional, and the test is performed by a professional laboratory and also interpreted by a professional laboratorian.

CLIA waiver assays are performed at a healthcare site but not necessarily performed by a trained laboratorian. Typically, microbiology CLIA-waived diagnostics are qualitative assays. Many of these assays are used at point of care in places like a doctor's office. CLIA waiver tests must demonstrate that they are simple and that they have an insignificant risk of an erroneous result. To demonstrate this, additional studies on top of what is required for a 510(k) are performed. So in addition to the 510(k) studies or analytical studies, we require flex studies and a near-the-cutoff study. Now, a near-the-cutoff study evaluates the performance of the assay in the hands of the intended user around the cutoff of the assay. So these are typically a C_{95} sample.

For over-the-counter tests, FDA proposes that we take some of what we do with the CLIA waivers and apply it to the over-the-counter tests. So we'd like to see a near-the-cutoff study performed by lay users, and we'd also like to see flex studies. For the clinical

study, we think it's important that the specimen is collected by the lay users, tests are performed by lay users, and the test is interpreted by lay users. In future slides, I will discuss exactly what a flex study is.

The FDA has approved or cleared several over-the-counter tests such as cholesterol, fecal occult blood, and pregnancy urine tests. However, there's only one infectious disease over-the-counter test where the patient performs the test, and that is the HIV over-the-counter test. All HIV tests are regulated by CBER, and this test was approved after extensive clinical and analytical studies following three separate Advisory Panel meetings. The FDA has also approved an HCV and an HIV over-the-counter test where the patient only does the sample collection, which is a blood spot, and mails the sample to the laboratory for testing.

So you may be asking, if the FDA already has reviewed and cleared over-the-counter infectious disease tests, why are the over-the-counter tests for influenza, group A strep, and chlamydia and gonorrhea different? The simple answer to that is that the tests we are discussing today are different because they are for different analytes. As I will present today, each analyte presents a unique risk-benefit profile that requires an individualized approach to evaluation. We have chosen to discuss influenza, group A strep, and chlamydia/gonorrhea because they can be used as representative organisms to evaluate other infectious disease diagnostics that the Division of Microbiology commonly reviews.

Next, I want to explain what information FDA will consider when we evaluate these over-the-counter infectious disease diagnostics. One of the main factors we look at is sensitivity and specificity.

Next, we also look at the positive and negative predictive values. These values are a measure of performance that combines the sensitivity and specificity of the test with the prevalence rates of disease. If there is a low prevalence of disease, even with very good

sensitivity and specificity, the likelihood of a false positive is higher than in a high-prevalence setting. This is most commonly seen with influenza diagnostics, which have a low positive predictive value outside of the influenza season, such as during the summer.

For these over-the-counter tests, FDA also wants to look at how well the test performs in the hands of lay users. It is not enough to demonstrate that the test performs well in a laboratory. The test must perform well in the hands of patients who will likely buy the test. To evaluate this, we will look at the likelihood of lay users making errors, such as errors due to device performance, compared to laboratory professionals; sample collection errors; errors following directions; and incorrect results interpretation.

Additionally, there are some standard risk mitigation strategies that FDA encourages manufacturers to take. Human factors engineering is an important part -- an important way for test developers to create a robust assay. Thought should be put into good test design, clear directions, and a robust procedure and easy-to-interpret results. FDA also thinks there is an important role for educational and supplemental material that is included in the package insert of the test. This gives the opportunity to educate the user about the risks and benefits of the test.

Along with risk mitigation strategies, FDA has considered the impact of potential over-the-counter tests on public health.

- Will a test increase or decrease the burden on our healthcare system? For example, will interactions with the healthcare community increase or decrease based on the results of the test?
- Will the availability of over-the-counter tests significantly improve access to testing?
- How does cost factor into this?
- Will over-the-counter tests affect testing in professional settings?

These are questions we want the Panel to consider in their deliberations later on in the day.

Next, in the following slides, I will outline the different selected benefits and risks for each analyte. They will touch on risks and benefits to individuals and to public health. This is not a complete list of benefits and risks but a highlighted selection that FDA believes are important.

First, there are some general benefits that apply to all three categories of tests. First is greater access to testing and earlier disease detection. With over-the-counter tests, there's a potential for patients to seek earlier diagnosis, and accordingly, earlier treatment. Earlier treatment can lead to potential reduced community spread.

Home testing may also decrease healthcare visits for users with negative results and lower-risk patients with positive results, such as a normally healthy person who has a positive influenza test. They might not need to go to the doctor.

Labeling and packaging also gives an opportunity to educate the user. It can discourage inappropriate antibiotic use outside of healthcare intervention, to basically discourage people from taking that leftover bottle of antibiotics in their medicine cabinet. It's also a means to avoid spread of infection and to educate users on how to appropriately reduce spread by either isolating themselves or engaging in safe sexual practices. And it also gives us a chance to educate high-risk individuals to seek medical care and potential treatment, regardless of the results.

Some risks that are associated with these tests are the risk of a false negative result. Now, risks of false results are dependent on the sensitivity and specificity of the assay, so that's one of the things that we want the Panel to consider. But the risk from a false result is that an untreated infection can prolong symptomatic disease and/or lead to complications, and if you don't know that you're positive, you have a false negative result, it

can also lead to increased community spread.

There are also risks to a false positive result. You could have unnecessary treatment with antibiotics or antivirals that could result in adverse effects. There could be inappropriate use of antibiotics, which we know leads to increased antibiotic resistance, and the patient may not seek treatment for the true cause of their illness.

For true positive results, there's also a risk because there's no linkage to the healthcare system. The test could detect colonized individuals who do not necessarily need treatment, and the patient may have a superinfection, for example, an influenza infection and also a bacterial infection, and they may not seek treatment for both diseases.

The risks that are specific to an influenza test have to do with surveillance. So there could be less professional testing that could impact surveillance activities. If fewer clinical specimens are collected and sent to laboratories, fewer specimens could result in a decreased tracking of resistance or detection of novel influenza viruses. In addition, if over-the-counter testing leads to less healthcare visits, there could be missing data on prevalence of influenza-like illnesses, which is a statistic that CDC uses to track influenza during the flu season.

There's also the poor positive predictive value when influenza has low prevalence. And this doesn't necessarily mean the summer, but it can also be during the flu season when there's actually low flu activity in a specific location. So it's not just isolated to seasonality but also to your location.

There also could be poor negative predictive value when the prevalence of influenza is high. If there's high influenza activity in your location, there's -- it's less likely that your negative is actually a true negative.

Some specific risks for over-the-counter group A strep tests is that the specimen collection may be difficult for untrained users. Currently, the posterior pharyngeal area is

the location that's sampled, and this area may be difficult to identify and/or sample and may lead to false negative results or adverse events. We know from current studies that it's very important to swab the tonsils and the posterior pharyngeal area, and if you don't swab the right location, the performance of the test is significantly decreased. There's also the risk that colonization may be assumed to be infection, so these people who are colonized don't necessarily need treatment.

Next I'm going to talk about the benefits of over-the-counter testing for STIs, mainly chlamydia and gonorrhea. So one of the best -- one of the biggest benefits would be greater access to testing and earlier testing. This could lead to earlier treatment and reduced community spread.

The over-the-counter availability has the potential to expand testing to individuals concerned about confidentiality who don't want to show up to an STD testing clinic, individuals who cannot readily access healthcare in their normal lives, and individuals who may want to test their partners, which was something that was seen with the HIV over-the-counter tests, that before a sexual encounter, people wanted to test their potential partners.

Some other benefits would be that over-the-counter testing would permit self-collection of genital samples as an option for both sexes, but specifically for women, which studies have shown is a desired option by a majority of women.

Labeling also gives the opportunity for user education: to review safe sex practices, the importance of testing for all sexually transmitted infections; and it could allow patients to access material that promotes sexual health and other educational activities.

Some of the risks of these tests would be a false negative result. An untreated infection in women can lead to complications and potentially ending in infertility. Patients may spread the infection to partners. If you don't know you're positive, you may not take

the same precautions.

False positive results also have significant risks. They can lead to unnecessary treatment with antibiotics and also potentially a significant emotional burden. A false positive result, especially in a monogamous relationship, has the ability to significantly impact those personal relationships.

A true negative result also has risks with it. A patient may interpret the result as a reinforcement of a high-risk sexual behavior; while engaged in this high-risk sexual behavior and my test came back negative, maybe that behavior may not be as high-risk as I thought it was. A patient may mistake this as evidence that they are free of all sexually transmitted infections; if you buy a test for just chlamydia, you don't want that person thinking that they're free from gonorrhea, syphilis, HIV. And a true negative result could also lead somebody to not get treatment for symptoms that they're having.

It could also impact surveillance activities. Both chlamydia and gonorrhea are reportable infections, and over-the-counter testing may not permit accurate disease tracking. Contact tracing is not possible for unreported infections. And obtaining isolates for tracking resistance may be impaired if all of these clinical -- if there is a decrease in clinical samples.

So one of the unknowns about over-the-counter tests for these analytes is how they will be integrated into medical care. The FDA would like to hear from physicians on the Panel as to how they envision these tests being used in their daily practice.

- How would you deal with a patient who comes to you with a positive test?
- Will results be accepted by healthcare providers?
- Would repeat testing always be necessary?
- Can and should over-the-counter results be captured in medical records?
- Are there ways for a test developer to encourage patients to seek appropriate

follow-up?

Next I want to discuss what is unique to over-the-counter diagnostics, and that's the user. How do you develop a test that can easily -- can be easily performed at home by an untrained user? Human factors engineering is very important for this because people have different abilities to follow directions. Lay users may not follow ideal laboratory practice by having a clean workspace and washing their hands before starting. Good quality samples may be difficult to obtain by non-medical professionals. And lastly, users may interpret results or the implication of results incorrectly.

To try and address some of these risks, FDA will require flex studies, which I will describe in a few slides, similar to what is required for a CLIA waiver. These studies will evaluate the risks of a lay user obtaining an erroneous result.

Before this meeting, FDA has put research and thought into the study designs for the analytical and clinical studies that should be performed for each of these analytes we're discussing today. Most importantly, I want to highlight the flex studies and the clinical study as two studies that are different from what is done for traditional laboratory tests. Flex studies need to demonstrate that potential over-the-counter tests are robust, and these tests may be unique to each product. A clinical study directed to the over-the-counter use testing should be conducted by patients in a home environment with careful attention to representative patient enrollment.

Flex studies are performed to inform the potential for erroneous results and the sources of errors for a given device, testing intended to challenge the assay procedure and test components based on possible deviations and variation that may occur with lay users. Examples of these test parameters are testing expired products, reading the results past the interpretation window, testing after the device has been dropped or dropped in water, and testing home contaminants, such as soap, hand sanitizer, and cleaning products. The goal is

for a robust testing process that has mistakes resulting in an invalid result and not a false result. This flex study approach is similar to that which is used for CLIA waiver evaluation. Flex study testing is performed by trained users in the laboratory to isolate individual sources of error, such as test system failure and operator procedural errors.

One of the main challenges to developing over-the-counter diagnostics for infectious diseases will be the specimen collection. Current specimen collection methods and sample types may not be appropriate for home use. A nasopharyngeal swab, which is commonly used for influenza, is probably too invasive for an untrained person to obtain. The pharyngeal swab used for group A strep assays may be difficult for home users, since obtaining a good specimen requires knowledge of the anatomy of the throat so the sample can be taken from the correct location.

In addition, sample collection methods may differ based on the patient population, for example, adults versus children, men versus women for STI testing, and for varying education levels. FDA would like to encourage manufacturers to research new sample types and collection methods that would be more appropriate for over-the-counter use.

Now I will talk about the basics of the clinical study for over-the-counter tests. For influenza and group A strep assays, we envision that the clinical study will recruit patients at urgent care, drugstores, childcare centers, and places where the true potential users of the tests will be. However, it is important to note that for the comparator assay, a healthcare professional should obtain the cleared sample type for the assay. The comparator assay should be a nucleotide-based amplification assay. Ideally, for the over-the-counter test, the patient should conduct the sample collection and testing at home or in a home-like setting, which basically means somewhere that there's not going to be somebody to answer questions for them and that maybe they have access to a sink with some soap and other kinds of necessary equipment and that the users interpret the results

and report them.

For STI testing, recruitment should be at urgent care centers, STD clinics, university health centers, etc. Patients should collect the sample and perform the test. A doctor or trained personnel can collect the reference sample for the nucleotide-based amplification assay. This is an example of a packet that North Carolina uses for self-collection for female genital swabs.

Some study design concerns that FDA has is that there is a need to recruit the true intended use population. The titer of an infectious agent may be different in those with symptoms severe enough to seek medical care versus those seeking over-the-counter medication or diagnosis. And patients already seeking medical care may not represent the over-the-counter test population in behavior, education level, and socioeconomic status.

This is something that's really important to the FDA. We think it's essential that over-the-counter clinical studies really recruit the right patient population. We feel that if you only recruit from a healthcare center, you may be artificially inflating the sensitivity or specificity, and you might not be getting a good evaluation of the procedure.

Lastly, I want to present to you the questions that the Panel will be asked later in the day. While you listen to the following talks from the CDC and the public comments, please keep these questions in the back of your mind for discussion.

Question 1: Do you agree with the benefits and risks described for over-the-counter testing of each of the pathogens, and are there any other benefits or risks that should be considered?

What measures would be appropriate to mitigate the risks associated with over-the-counter diagnostic tests?

What would be recommended minimum performance criteria for testing of each pathogen?

Please discuss recommendations for ensuring that individuals representing the appropriate intended use population are enrolled in the clinical studies to demonstrate the device performance and support over-the-counter claims.

And please discuss appropriate ways to connect patients to healthcare services. Are there any recommendations regarding potential patient access to additional resources that diagnostic test manufacturers should be responsible for, such as a hotline? Does this differ across the diseases? So is this different for influenza as opposed to an STI?

Lastly, I'd like to acknowledge my colleagues, the over-the-counter working group in the Division of Microbiology Devices, the Division management, and the Office management.

Thank you very much.

(Applause.)

DR. PETTI: Thank you, Dr. Conenello.

I was covering for Dr. Angie Caliendo, who has now arrived, and I will hand over the meeting to our Chair.

DR. CALIENDO: Thank you for covering, Cathy. I appreciate it.

So does anyone have any questions for Dr. Conenello?

DR. NOLTE: Rick Nolte.

The flex studies thing is basically a failure mode analysis. Is that basically what we're talking about?

DR. CONENELLO: Yeah. Normally, we require the flex studies to be conducted either to failure or to kind of an exorbitant amount. You know, if it called for one drop and your test doesn't fail after 20 drops, we're not going to require you to test to failure. But yes.

DR. HARRELL: Lizzie Harrell.

You have a slide on the risk of an over-the-counter test for group A strep, and it

mentions that colonization may be assumed to be infection. Are you saying that, of the organism, if they get a test and -- I'm trying to understand what that comment means.

DR. CONENELLO: So basically, somebody could test positive when they're colonized, and a colonized person doesn't necessarily need to be treated. They may not have a symptomatic infection that's causing problems, and so somebody who probably doesn't need to be treated with antibiotics --

DR. HARRELL: Right.

DR. CONENELLO: -- could be positive.

DR. HARRELL: I was thinking, in that case, maybe if you assume that you're going to try to swab the tonsillar area to look for group A step, but if it's there, if there's a possibility of it being somewhere else, to me that was not a big concern about it being colonized in some other part of the oropharyngeal area.

DR. CONENELLO: Certainly, also a mitigation would be having to see a medical professional in order to get an antibiotic prescription, who would be able to evaluate your symptoms.

DR. HAMMERSCHLAG: I just want to give you a little idea, though, of the marriage here to that. If you line up a hundred children coming in with a sore throat and you do a throat culture on them, about 30% will be positive for group A strep, and colonization rates or carriage rates actually in some school-aged children may exceed 30%. And if you were then to take that 30% and actually do antibody-determined infection rates, it's probably less than about 50%. You can't make a clinical diagnosis.

So even now we're over-treating quite a bit. But one other thing I want to say about doing a posterior pharyngeal swab: We've been told that if you want to really get a good, adequate sample, you have to get a piece of the tonsil on the swab and have to go to three places. And looking at that, I doubt any layperson can do that, quite honestly. You'd have

to get the tongue down; the kid has to be cooperative. Obviously, somebody is not really going to be able to do this on themselves, and actually, it makes collecting -- self-collection with a vaginal swab for chlamydia and gonorrhea look like it's a piece of cake compared to this.

DR. CONENELLO: Yeah, I think that's -- group A strep is specifically one of the assays where we would really encourage new specimen type development. Whether that's possible or not, I'm not sure.

MR. SIMON: Being a consumer advocate, I'm talking about how well the test performs in the hands of lay users. The two things that concern me is the degree of risk, in other words, what can happen and the percentage of the people who it can happen to. You mentioned sample collection errors, errors following directions, and correct result interpretation. Is there a percentage that's acceptable, because nothing is for sure or positive, but is there a percentage that's acceptable depending upon which test you're talking about?

DR. CONENELLO: So I think that's one of the things we want the Panel to address is performance and things like not following the procedure correctly. And not getting either an invalid or a false result would be captured in the clinical performance. And we always look at also the invalid data, so how many invalid tests. If we see a test and they have 1,000 people tested and 150 people got invalid results, we're going to take note of that. But if the Panel wants to speak to a specific invalid rate that's unacceptable from following the procedure, we'd be welcome to hear that.

DR. CALIENDO: Go ahead.

DR. MARTENS: Has the FDA looked at, or is it within their purview to look at, what the collateral testing is going to be? You know, the STD is easy. If you ask for the partners to get tested, do they get tested with the over-the-counter test? Do they go to a physician?

The other thing is how long. You say over the last 6 months, all partners at 3 months. And it would even extend to group A strep if you'd say, you know, do you have their siblings tested and during what duration of their disease? So has the FDA looked into that?

DR. CONENELLO: No. We've kind of searched the literature, and there is not a whole lot of information on over-the-counter testing, simply because they're not out there. So there haven't been a lot of studies done on the impact of over-the-counter tests because there really aren't that many.

DR. CALIENDO: Let me just remind people, when you speak, to please introduce yourself each time so it's easier for the people who are actually recording for the --

DR. MARTENS: That last question was Mark Martens, Rutgers and Robert Wood Johnson.

DR. CALIENDO: Are there any other questions?

Go ahead, Kim.

DR. HANSON: Kim Hanson, the University of Utah.

From a historical perspective with the over-the-counter HIV test that's performed and interpreted by individual patients, was there any -- it seems like the flex studies are more geared towards understanding instrument or test failures, either user or the instrument itself. I'm assuming that all of these tests will need a substantial kind of educational materials that go along with them to educate the users about what to do with a positive or a negative result. Is it anticipated that clinical studies will also need to gauge how understandable those instructions are and whether it impacts behaviors?

DR. CONENELLO: Sure. So for current over-the-counter tests that we talked about, like cholesterol and pregnancy and things like that, there is a part of the review that looks at a questionnaire to the users on how easy was the test on a scale of 1 to 5, and you know, did you find the test procedure easy to do, were the directions understandable, and that

kind of thing. So that's something that's standard that's done now with over-the-counter tests and that we would continue to do. So there is that. And then we also encourage companies to do sort of a pilot study in evaluating their tests and the directions and get feedback as part of human factors engineering before they go into the final clinical study.

DR. CALIENDO: So Angie Caliendo.

Is there any way to, during a clinical study, determine how well people followed the directions? Can you independently have them do it in front of people or something like that?

DR. CONENELLO: So we have discussed kind of a one-way mirror situation, but at the same time, then you're taking the testing out of the home. And so I think it's kind of a balance of do you want the testing from the clinical study performed in a home environment where there's all the correct distractions, or do you want to see exactly where the errors are being made? And I think we've kind of landed on the side that we'd rather have all the distractions of the home environment and leave maybe the pilot study up for observation.

DR. HARRELL: Still talking about the educational part --

DR. CALIENDO: I'm sorry, Lizzie, please --

DR. HARRELL: Lizzie Harrell -- educational supplemental material included with the test, I was going to make a comment that it needs to be simple but short, because when directions get to be too long, I don't think laypeople are going to take the time to actually follow it.

And the second thing is did you consider any PSA announcement? If this is going -- if this comes to be and we're going to start having these kinds of tests on the market, would some PSA announcements that would be broadly seen by the general public prepare them for this and get them ready to understand what they are in for?

DR. CONENELLO: I'm not sure that the FDA normally makes public service announcements like that, but I think it would be up to the company to kind of let the public know about that.

DR. GITTERMAN: If I could just make a point: (1) It's a regulatory mandate that the test be simple to use, and (2) to address something that Dr. Caliendo -- well, two previous questions. One is there are user comprehension studies that people can do. The question is where you set the bar. But usually again, it's set, you know, eighth grade, seventh grade, but there are standardized methodologies for doing that. Again, you have to get the user to read it, so the studies may not address it. I mean, how many have read a package insert that they get from CVS?

And the question you asked earlier, Dr. Simon, is a very good one. Nobody knows if those numbers existed, and we published them in the same way, you know, like in the example of HIV, which I have to say I'm not completely familiar with. But my understanding is that the home-use tests are not as sensitive or as accurate as a test you might get from a laboratory test, a laboratory-based test. But in that context, the public health benefit by capturing people who wouldn't otherwise get tested; otherwise, it may outweigh the benefits of -- losing a little bit on the test side.

So it's really -- you know, those numbers may differ, and I think, as Dr. Conenello mentioned, that's some of the advice we'd like to hear from the Committee. There's no number to say that the adverse events might outweigh or would not outweigh the benefits of given devices, or that the availability of having the tests, in fact, outweighs perhaps better performance as you might expect for the laboratory professional. But I think an important point Dr. Conenello made is it differs for every analyte. Otherwise, we would've just accepted previous precedents.

DR. HENRICKSON: Kelly Henrickson.

I think that's critical. So for HIV, it makes sense from a public health standpoint. I think that the majority of children and adults who are infected with influenza are going to be mildly infected or asymptomatic, and that's the population that really is going to be tested by this over the counter, and that's the population that probably doesn't need to be tested and/or wouldn't seek medical help anyway. And so I think there's a big difference of the public health risks involved.

The other thing, I guess, I wanted to throw out is I think it's critical, like you said, to test these in the real-world situation, and that's going to be incredibly hard to do, as you mentioned. You mentioned the problems of bias that enter anytime we try to do studies on these things, and trying to get a bunch of people who would buy this over the counter but who aren't the people who would normally go in and seek medical care are the population. Maybe an app on the phone, you know, where you give away the test free in centers in cities, and all they have to do is push on an app to say it was positive or negative or something to get some kind of result back.

DR. CONENELLO: I think manufacturers would welcome any recommendation that the Panel has for app development or, you know, recruitment for clinical studies.

DR. HENRICKSON: But it's going to be -- that's going to be incredibly difficult.

DR. CONENELLO: It is going to be challenging. Something I don't know that I mentioned is we'd also like the Panel to think about bias introduced by a physician collecting a sample before a patient. This has been something that the FDA has discussed for a while. So in the case of a pharyngeal swab, if you don't know where your tonsils are, but the doctor swabs your tonsils first and then you are told to take a self-sample, is there some sort of education there involved with the physician collecting the sample first? And we'd like the Panel to discuss whether that's a real perceived education bias and if we should make requirements.

DR. HENRICKSON: Kelly Henrickson again.

I think that no matter what, we can't educate people to do this, in my opinion. I mean, I think that you're going to have to show that any kind of touching of the oral surfaces or the nose -- I mean, no matter what you say about swabbing, they're going to do it in a million different ways, and I think there's no hope that you can --

DR. CALIENDO: Okay, we're going to have time to talk about this in the afternoon. I'm sorry to cut off the questions, but we'll come back to deliberations.

Dr. Conenello, thank you so much for your presentation, but we need to move on to our next presentation, and that will be done by Dr. Gail Bolan. At the conclusion of this presentation, we're going to have a short time for questions, also.

So thank you, Dr. Bolan.

DR. BOLAN: Thank you very much. Good morning. For the record, I'm Gail Bolan, and I'm the Director of the Division of STD Prevention at the Centers for Disease Control, and I was asked today to not give you a complete overview of the tests that don't exist yet, but how we sort of think, from a public health perspective, of identifying asymptomatic infections, which is really a challenge for us in the field of sexually transmitted infection because the vast majority of our infections are asymptomatic. So people don't know they're infected; they're not accessing care. A lot of our providers don't think about them and do not test appropriately. And then we also have some challenges with our surveillance system.

So with that, let me give you an overview of things that I'm going to just discuss. And obviously take down notes for questions during the question and answer period. I just want to give a general overview of chlamydia and gonorrhea. That was really the focus of today. So I'm not getting into the syphilis. And there is one point-of-care test available for syphilis, treponemal testing, in the United States, and many are available globally. And the

HIV and hepatitis C tests have already been mentioned.

Just a little bit about chlamydia and gonorrhea epidemiology and also sort of the limitations of our case-based surveillance systems, even though we use them for very important work. The strategies and approaches that we take generally in STD prevention and control, and I really want to focus on our screening approaches, which means identifying asymptomatic individuals, not diagnostic testing where we're actually testing symptomatic individuals, but our screening principles and recommendations because I think it will have some implications for when we're thinking about people accessing over-the-counter tests. And then we also try to look at things from a supply, demand, and kind of patient adherence frameworks, so we'll talk a little bit about that. And we're even trying to improve our supply and improve our demand and improve our patient adherence to not only being tested but making sure that they get treated and that their partners get treated.

And then sort of what have we learned from sort of outreach screening that's been done in public health? And we've got some great work that I'll share that Dr. Gaydos has done, looking at sort of online opportunities to increase access to screening, and then a little bit of innovation that people are looking at for increasing access to timely treatment. And then I'll just give you sort of an overview of sort of the risk and benefits, from my perspective, with over-the-counter gonorrhea and chlamydia tests. And some of those were already mentioned in the great overview we just heard.

So for those of you who haven't thought about sexually transmitted infections, we do like to think that we were the first hidden epidemic because most of our infections are asymptomatic. Actually, 63% of gonorrhea and chlamydia occurs among young sexually active people between the ages of 20 -- between the ages of 15 and 24. So that is our main target population, and it has some implications in terms of accessing tests when you're younger and have other things that you're thinking about. And I would also like to say that

not all of our young people are sexually active at very younger ages, and so therefore our rates of disease are incredibly high in this population. We also see a disproportionate amount of gonorrhea and chlamydia among sexual and racial and ethnic minorities, and that's gay, bisexual, and other men having sex with men, as well as significant health equity issues among African-American populations in the United States.

We're concerned about these infections because the adverse health outcomes are predominantly in women, related to upper tract infection caused by pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, and infertility. And there's now more evidence that actually on an individual level, gonorrhea and chlamydia, especially at the rectal site, facilitate HIV transmission and again were the high-volume reported conditions in the United States. Gonorrhea and chlamydia alone, the top two reportable conditions to CDC, account for 85% of all the reportable conditions that are reported to CDC in the United States.

Now, just sort of looking -- my colors did not come out adequately here, but just sort of looking at our estimates of sexually transmitted infections, you can see that the prevalence of gonorrhea is about 270 -- this was done by a study that Catherine Satterwhite did a number of years ago, and it was published in 2013, and our prevalence of chlamydia is estimated to be about 1.5 million cases. Those are actually from our case-based surveillance system and from some NHANES studies where we get national estimates of prevalence. But because we recognize that a lot of infections are not detected, we estimate that there's more like 2.8 million cases of chlamydia annually and about 820,000 cases of gonorrhea. And you can see that we have a lot of other sexually transmitted infections, both bacterial, viral, and parasites, and there's significant cost to these infections to our society.

We view case-based surveillance in STDs as sort of our core function and backbone

of public health. Nobody else does surveillance in the United States. We like to think that our case-based surveillance is population based because we do use it for public health action to reduce morbidity and to improve population health. Our case-based system -- this is true of all reportable conditions in the United States -- are authorized by state legislators, not by CDC, at the federal level. And we're working with CSG. We are privileged to obtain some of these data that are required by law to be reported to state health departments and are carried out by the state public health officials.

We decide which conditions to make reportable by our criteria for public health importance. There are seven criteria that we look at to decide whether something is of public health significance, and it includes things like burden of infection; we want to have a high level of frequency of the condition; certainly adverse outcomes, health inequities, costs; preventability, you need to be able to prevent the condition; communicability; as well as having some public interest in the health event of concern.

Now, we actually, in STD -- and this is also true for HIV in our center and, I believe, viral hepatitis -- actually use our case-based surveillance to allocate funds. So when we're starting to talk about challenges of over-the-counter and possibly no reporting of these cases, there are some concerns that we could actually be misaligning our funds. So the formula that we use in the STD division is we recognized that we didn't want to only allocate by number of cases, and that's what HIV does, basically AIDS cases originally and now it's HIV cases is what's used in the formula of allocating our HIV prevention dollars in the United States.

We use 50% of our allocation to the number of cases, but then we also had some of our middle-sized states arguing that rates actually matter, too. So we made a proportion of 80% cases and 20% rates because we found that if we use too much rates, then we were disproportionately giving a lot of our money into small states that had small numbers and

small denominators. But we also wanted to recognize that a lot of our at-risk populations are not getting tested, and so therefore only relying on cases would be a little bit unfair. So the other 50% of the allocation is looking at at-risk populations, which we defined as sort of the old definition of reproductive age, from 15 to 44 years of age. So I think this is an important point, that we do use our surveillance data for public health action as well as for funding and other targeted interventions.

Just to see what's been happening with gonorrhea and chlamydia in the United States sort of after a number of decades of decline, at least of gonorrhea, we've seen significant increases, looking -- I don't know if I've got a pointer here -- from 2014 to 2015, of gonorrhea cases increasing. Our surveillance report that came out in 2014, one of the important points was that it was the first time in a couple decades that we actually had increases in all of our reportable STDs; that's gonorrhea, chlamydia, and primary and secondary syphilis.

Some of the increases that you're seeing in chlamydia, though, from the early '90s to current, actually is a reflection not of possibly increasing incidence but more a reflection of over this time more people are reporting cases of chlamydia. They're becoming reportable by law in most states. Also, technology was changing, and we started using more sensitive tests. So therefore, obviously, we were picking up more cases. So we're a little bit challenged to really understand the interpretation of these curves, as to whether they are truly representing increasing incidence or whether they're a reflection of reporting and technology artifacts. But we are concerned about these recent increases we've been seeing in the last couple years, and there are some data suggesting that, at least among gay men, incidence is increasing.

We also use the National Health and Nutrition Examination Survey to look at prevalence of chlamydia. Unfortunately, gonorrhea is too infrequent to test for. In

NHANES, the sample size is not large enough. But chlamydia is a very age-dependent disease, and we see the highest prevalence in the purple bar of 6.8 in the 14- to 19-year-old age group. It declines to about 3% in the 20- to 24-year-old age group and then continues to decline with age. And this gets into the challenges of screening low-prevalence populations and ending up with more false positives than true positives as women get older. We also, you can see here, have highlighted the African-American rates among teenage girls at 16% and 12% in the 20- to 24-year-old age group.

The things I mentioned about the limitations of our case-based reporting system is that we know that even though it's required by law, many providers do not report cases to us. They think that that's the laboratory's responsibility and it's not the provider's responsibility in their state. We also note that a lot of providers, to save cost, actually will presumptively treat patients, either a contact or someone with symptoms, and not get the diagnostic tests. So we never really know if that urethritis is a case of gonorrhea or chlamydia. We just know that they were presumptively treated for those infections, so that limits our ability to record those cases in our surveillance systems.

Our biggest problem, as I mentioned, is most of our infections are asymptomatic, so our patients don't access care when they're infected. And we still have problems with a lot of providers not screening according to national recommendations to the populations at most risk for chlamydia and gonorrhea.

So we believe our case-based reporting system really reflects those who access care and get tested and get reported to the public health system. We also have limited data that comes with our case reports, so we are limited in our epidemiologic analysis.

Moving on to sort of the strategies and approaches for STD prevention and control. I think we all recognize that one of the drivers of transmission in the community is sort of your sexual and social network, and we're actually starting to look more at molecular and

whole genomic sequencing in ways that we can better identify transmission dynamics and points of transmission, especially because of our concern of the threat of untreatable gonorrhea.

But our strategies and approaches for us to do prevention and control really haven't changed since Thomas Parran wrote the *Shadow on the Land* back in the '40s. We basically want to be able to prevent people from ever becoming infected with sexually transmitted diseases, and that's through health education and promotion, behavioral interventions, and vaccination.

And we do at least have two vaccines, HPV and hepatitis B, which are sexually transmitted. I would say that we spend most of our resources on detecting infection, which is screening asymptomatic individuals. Obviously, we want to make sure we've diagnosed the symptomatic persons as well, and then making sure we link them to care. And obviously if you come to an STD clinic, you're already there, you're going to be treated there. In some ways, an STD clinic is sort of an early form of a sort of over-the-counter test. It's really where people have gone in our society to get confidential testing and not have their parents or their primary care provider know of what some people consider very stigmatizing and embarrassing conditions. We also want to make sure that we don't just detect. We need to make sure that we're treating our patients and their partners and that cases are reported to public health.

When I talked about our framework of wanting to increase supply, we've worked hard at improving the healthcare system to have testing available for at-risk individuals. We also augment that with public health outreach programs through mobile vans and other venues and contact tracing programs. So we really also look at the over-the-counter home testing as a possible way of increasing supply for at-risk intended use populations, but obviously, as has been discussed, there's a lot of studies that need to be done to see how

this actually looks at it from a risk-benefit perspective.

We've been trying to increase demand for screening by working with the healthcare system again, and healthcare providers. We are not doing as well as we would like to be. And we've also been working with empowering at-risk individuals. We've had a fairly robust what we call "Get Yourself Tested Campaign" that's been going on in college campuses and for youth around the country, empowering youth to be empowered to come in and be proud that they're actually asking for a chlamydia test or a gonorrhea test.

We also want to make sure that patients adhere to what we call the cascade. So we don't want just screening to be happening. We want to make sure people, you know, get screening done so that you have earlier diagnosis, but most importantly, that screening will prompt timely treatment of patients and their sexual partners, to improve health outcomes and reduce community transmission. And again, my last comment is you've got to report those cases to the department of public health.

So moving on to the screening and diagnostic principles. There are a lot of providers that don't really understand the differences between screening and diagnostic testing. And basically, screening is to test apparently healthy people to find those who are infected with an asymptomatic infection, and diagnostic testing is really to assess signs and symptoms and patients' complaints and find out what are causing those signs, symptoms, or complaints.

There was a wonderful article, if you haven't read it, by David Grimes. It was published in the *Lancet* in 2002. It actually is titled "The Uses and Abuses of Screening Tests." And so I think some of the analogies here could be considered for sort of over-the-counter tests that -- you know, unfortunately in some providers' settings, once people recognize that STDs are a problem, they tend to test all of their patients. I've had some providers tell me that I don't want to have any of my patients not be diagnosed with

chlamydia or gonorrhea, so they test women up to the age of 60 in their clinics so that they think they're not missing any cases. But our tests are not that perfect, and actually over-screening can be harmful. And when you're dealing with STDs, you've got concerns about stigma, you've got concerns about relationship issues. Certainly you've got concerns about cost, and we've got concerns about overuse of antibiotics because of the STDs we're talking about today. Their treatment is with antibiotics.

Another nice outline of why we screen and when, "Is Earlier Diagnosis Worth the Cost?" was published in *Clinical Epidemiology: A Basic Science for Clinical Medicine*. And basically, why don't we find these earlier infections if we can do something about them and it's going to improve survival or quality of life? Certainly, the clinician and the patient has to have time to manage the diagnosis before the complications develop. The big question is if the patient has an earlier diagnosis, will they comply with the intervention? And the intervention we're talking about here is treatment. And has the effectiveness of the screening program been established? And also, has the cost effectiveness and accuracy been established, as well as is this procedure or approach acceptable to both the patient and our society? So these are kind of the criteria we use when we're thinking about our screening recommendations that we put out from the CDC, as well as U.S. Preventive Services Task Force also puts out national recommendations for screening.

So clearly we want to have screening programs that are cost effective, and it depends on prevalence, the test performance characteristics, the sensitivity and specificity of not only the screening criteria but also the diagnostic tests. And then there's cost and the cost of treatment and complications.

So the ideal screening program, and maybe this is what we would say is also the ideal over-the-counter program, is we want to make sure that we're testing the right population, you know, with the right infection. And for the infection, we want to make sure

there's high morbidity. It's likely to be asymptomatic, and that early detection and treatment reduces complications and improves health. We want to have the right tests. Ideally, we want noninvasive, inexpensive tests that are acceptable to patients, that they're easy to collect, transport, and the lab can run with high accuracy. And we also want to make sure these tests are very sensitive and specific. And overall, we're looking for a cost-effective intervention in terms of population health.

So as I mentioned, we at CDC put out screening recommendations that are evidence based in our STD treatment guidelines. We recognize that you can't treat unless you know how to diagnose first, as well as the U.S. Preventive Services Task Force has STD screening recommendations. And we've actually harmonized our recommendations with them, and we had a few years that were differing a number of years ago.

So in terms of chlamydia and gonorrhea screening, this is who we now recommend should be tested if they have asymptomatic infection, and I'm mainly highlighting non-pregnant women and men who have sex with men. So it's currently recommended that all sexually active adolescents and women less than the age of 25 be screened annually for chlamydia and gonorrhea.

It gets a little more murky when we're talking about "older women" over the age of 24. Guidelines use sort of vague terms like "if increased chlamydia or gonorrhea risk." The risk factor studies have not been done more recently, but at least it's generally accepted that if someone has new or multiple partners in the last year, that they're at higher risk. If their partner actually has concurrent partners -- and this is for women -- if a woman thinks that her partner is likely having sex with someone else while they're in a relationship with that partner, that's been a risk factor at least for chlamydia infections. And obviously if their partner has been diagnosed with an STI.

We're also recognizing, though, that a lot of times clinic prevalence and community

prevalence varies in this country, and there are some clinics that have higher prevalence in older women, so they increase the screening threshold for when they screen. And we also know that we've got some communities with very high prevalence of infection, and we're encouraging providers to know their disease patterns in their communities so that they can screen appropriately if they're in a high-prevalence community.

For gay men, we know we have high prevalence of STIs among sexually active gay men, and you really need to know site of exposure. So we recommend at least annual chlamydia and gonorrhea screening for sexually active gay men, and more frequently if they're at high risk, which usually is a lot of anonymous multiple partners and substance use, especially methamphetamines has been associated with high risk of STIs. And we recommend screening both the urine for chlamydia and gonorrhea. We recommend rectal screening for gonorrhea and chlamydia if they'd had receptive anal sex. And we only recommend pharyngeal GC screening if they've had receptive oral sex.

This gets a little complicated because our tests are really bundled now. So you usually get the chlamydia result anyway, and most providers don't want that result turned off, even if they didn't order it. And there's a general feeling that, you know, chlamydia is not that pathogenic in the throat. There's the whole lymphatic system that probably clears any organisms. But I have to say, when I started in this field and didn't know anything about STDs, I was told a lot of things about STDs that I tried to look up in textbooks and never found the answer to. So I still think the story of chlamydia in the throat may not be fully understood, and we'll probably learn more as we do more pharyngeal screening with the bundled tests.

So then we always get the question, well, what about screening heterosexual men? And again, there are a lot of providers that do because they just think, I just want to be testing everybody and making sure no one has these infections. But generally, we at CDC

do not recommend screening heterosexual men for chlamydia or for gonorrhea, so that's going to pose a challenge when you're dealing with over-the-counter tests. On a broad-based population level, there's really no documented substantial secondary prevention in women, and that's for what the cost of chlamydia and gonorrhea complications are. So we do sort of have some vague recommendations if you're working in a high prevalence clinic like corrections/detention facilities for youth, STD clinics, and teen clinics. You might want to consider routinely screening all young men that come into those clinics.

But again, the definition of what's high prevalence is not well defined either. I used to ask that question when I was in California and came to my CDC advisory panel, and they'd say, oh, the STD director knows the answer to that. And I said I am the STD director. I don't know the answer of what high prevalence is. So obviously some of these need to be studied.

So for heterosexual men, we really, really want to focus on partners of infected women. I mean, that's how we really look at who's at greatest risk for these infections and who should be tested and treated.

The good news is we actually have some good tests for chlamydia and gonorrhea: nucleic acid amplification tests. Our lab and also with the help of Drs. Gaydos and Van Der Pol here, you know, were involved in the publication of our lab-based detection of chlamydia and gonorrhea that was published in 2014. These tests are highly sensitive and highly specific. Studies have actually shown that the optimal specimen is the first-catch urine in men.

And actually, women do a better job of collecting vaginal swabs in the clinic than the provider does, in general. Now, obviously if a woman's going to be having a pelvic exam and if she's got symptoms, I think that's a time where most providers still will do an endocervical swab. But really, the field has moved towards vaginal swab, especially self-

collected vaginal swab, for women.

Our challenges have always been, and still remain, that while we're recommending rectal and pharyngeal testing using NAATs in predominantly men -- although now we're recognizing some women also have high prevalence of rectal infection and pharyngeal infection -- these are not FDA cleared. So a number of labs, including Quest, have done validation protocols so that they can be available for clinical results. And once the rectal and pharyngeal tests were validated for clinicians collecting the specimens, now a lot of providers have actually moved to actually doing self-collection at sites because the exam can be expensive and a lot of people are asymptomatic. And so express clinics are now being designed where people can come in and collect their rectal or pharyngeal. And actually, people seem to do an okay job on the pharyngeal collection compared to what I'm hearing about group A strep.

So I think that our practices are ahead of where the FDA clearance is for these tests. Obviously one of the challenges, because of our concern about resistant gonorrhea, is that these NAATs tests -- we do not yet have any molecular markers. There's one test that's being evaluated for ciprofloxacin susceptibility. So without a culture, we really do not have an understanding of what the antimicrobial susceptibility is of the GC strains circulating in our country through routine screening. We do have a surveillance system that's been monitoring resistant gonorrhea for quite some time in selected STD clinics.

I did want to make one other little comment here, although I know we're not supposed to be talking about the other type of over-the-counter, which is when you need a prescription. But we also recommend, because of high rates of reinfection when partners don't get treated, that after chlamydia and gonorrhea and trichomoniasis, we do recommend a repeat test at 3 months. And clearly we know, at least for chlamydia, that the second infection and third infection causes significantly more harm in the upper tract

for women.

And this is just showing you the relative risk of PID and ectopic pregnancy after the second and third infection with chlamydia. And these infections tend to be asymptomatic. So we're really, really trying to get people back at the 3-month time interval to get tested, and a lot of people really don't want to come back into the clinic and take time for that visit. They'd much prefer to collect their specimen at home.

And we also know that rates of reinfection -- this is a review of 17 active cohort studies of both chlamydia, and the graph for gonorrhea looks exactly the same. Reinfection just continues with time until you get up to your 12-month annual test. So we really want people to -- we sort of picked 3 months as a good breakpoint of where we want people to get retested to see if they've been reinfected, which means they need to be retreated.

So again, this sort of just raises that question of there is a need for people who've been in the clinic setting, they've had their test collected in the clinic setting, either by themselves or by their clinician, and then they've got that 3-month test that they need to obtain. And it would be great if that was an option for -- at least a lot of patients have said to me they would prefer to just be texted and say it's time for your chlamydia test, just go get it somewhere and do it at home and mail it in, because the vast majority of the tests actually turn out to be negative.

I'll just talk a little bit about interventions to increase our chlamydia and gonorrhea screening and treatment and what we've learned. And I'm going to talk a little bit about what we've learned from screening in the clinical settings, the sort of community outreach public health settings, and then some innovative work that's been done with online or smartphone outreach, which is "I Want the Kit."

So unfortunately -- this is looking at our HEDIS data, which measures screening coverage among sexually active women by age and either by Medicaid plans or commercial

HMO plans -- we've had slow uptake. We look a little bit like the HPV vaccination, you know, starting in 2001, when chlamydia became a HEDIS measure, but we're concerned about sort of the declining Medicaid screening rates in 16- to 20-year-olds and sort of plateauing of the 16- and 20-year-olds in HMOs. And certainly we're not even up to yet 60% of all young people who really need to be tested are getting tested. So it shows we've got a huge public health need to get more people tested, and our traditional clinical system is not providing at least those tests to everyone who accesses care.

There's been a number of studies looking at why we are -- you know, chlamydia screening isn't as high as we would like it. I'm not going to go into all of the provider knowledge and attitudes that are prohibiting women to get the test that they deserve, but we also know that clients have some concern, especially around stigma and embarrassment. A lot of young girls are very anxious about pelvic exams and have not found them to be a pleasurable experience when they go into the doctor's office.

Adolescents also, and even some younger people, younger women, have concerns about confidentiality and also explanation of benefits, where the bill goes home to the parents and it says that they had a chlamydia test. And then partly because now we have a lot of younger people on parents' insurance, and once you're on an insurance plan, you have to pay the deductible and the co-pays, we're hearing that there are some younger women not getting screened and don't have access to free testing like they used to have in college because they're required to use their parents' insurance, and then they're also being charged high co-pays and deductibles.

And we've got some other factors going on. Healthcare visits for adolescents are changing because the Pap smear recommendations have changed, and also increasing use of long-acting contraceptions may limit the number of visits, where we used to use them as opportunities to get chlamydia screening done.

So what have we learned about our community outreach screening programs? A lot of this is just work that gets done by health departments. It never gets written up. Everyone kind of just writes it up in their grants that they send to us at CDC. There's been a lot of mobile van efforts. There's been a lot of venue-based screening where people went to pharmacies and tried to have people be screened. When they came in for their emergency contraception, they got a little swab to screen. There's been bar screening, health fairs, hair salons. We also have our disease investigation staff in the public health department to go out and do field-based screening. When they're doing contact tracing, they'll actually bring specimens to the field, as well as medications to the field. But in general, these approaches have been pretty costly. Generally, you find a lower-prevalence population when you sort of do these broader-based screening efforts.

We also are being challenged by the eroding infrastructure of our public health system, especially in STDs. We've had many STD clinics close over the last decade, as well as our DIS workforce is much less than it was. So we really don't have the staff just to go out and do contact tracing for chlamydia and gonorrhea. Most health departments can't even keep up with syphilis anymore, and that's pretty much what they focus on. So it's not really being done actively for gonorrhea or chlamydia. And then the other challenge is it just really was just reaching a limited number of individuals in a given population. It wasn't really having huge reach or scale in the target population.

So I tried to summarize Dr. Gaydos's work all in one slide because she's done some amazing work, starting in 2006, on looking at ways that the Internet can be used to have people access testing by ordering a kit and then having it sent to them and then they mail it back in to the lab at Hopkins.

And just sort of summarizing the last 5 years of what's been happening with "I Want the Kit," in general, the number of requests and tests, I would say, from a population-based

standpoint, not huge. On average, there's been about 3,000 requests a year, and about 1,700 swabs were actually tested. The response rate again has been challenging. Even when people request a kit and they get it, they don't return it, and the range has been from 42 to 65%. Also, it was started as a research project, so there are a lot of additional barriers that don't normally happen in the practice setting, like a research coordinator would contact the person first, before they would mail the kit, to make sure that they consented to be in the study.

But the good news is I think a lot has been learned about how acceptable, you know, collecting swabs at home are through this research study. All the men and women -- the studies evolved, even doing penile swabs now in men -- have consistently reported that it's easy to collect these swabs. Women have stated that they actually prefer to do their own swab at home. And in general, when there's been head-to-head comparisons comparing a clinician-collected specimen to a patient-collected or an individual-collected specimen, the test performance characteristics of the NAAT test for chlamydia and gonorrhea seem to be the same.

These studies also, though, have been challenged from the treatment side, like we don't really know who's getting treated in a lot of the studies because the focus has been on getting people tested and getting them their result and then counseling them about how they can get treated.

You can also go online now and just look. There are a lot of Internet sites that offer STI testing. And it's very hard to find out what the services are and whether there are privacy issues and what information are they collecting and are they reporting to health departments. A lot of them are offering panels, you know -- you know, you don't have a choice. You get 8 to 10 pathogens, and it's pretty much testing for all STIs that are possible to test for. And they tend to be pretty pricey, over $100 for some of these panels. So it is

interesting. These have been around for a long time, but it's been difficult to contact them and try to get information about volume and age group and positivity rate. So that's all that I can say about what we know about those sites.

I do want to talk just quickly about point-of-care testing because obviously if you're talking about an over-the-counter test and you want somebody to be able to run it at home, that's kind of the point of home care. Clearly, this is something that we really -- clinicians and patients really want to have available in the healthcare setting. So maybe an over-the-counter test will actually help us have better point-of-care testing clinically as well. There aren't many that are very accurate that are out there right now, and there are not many that can be performed in a short period of time to really be considered point of care.

There's a lot of theoretical advantages, and we would say this would be advantages you can think about for over the counter. Obviously faster results means more timely and correct treatment, reduced waiting in clinics and follow-up visits, reduced presumptive treatment, less patients lost to follow-up, more targeted prevention counseling, and patients may be more likely to comply with prevention interventions.

Hopefully, if you're doing timely treatment, that you're decreasing community transmission because people aren't leaving your clinic not being treated, waiting for the test result, while they're still infectious, and they have to wait a couple of weeks until the test result returns positive and then they get back in for their treatment. It certainly can make your clinic practice be much more efficient and cost effective, and we hope that they also improve medical outcomes.

There has been some assessments about what kind of, you know, point-of-care tests do clinicians want. Most say they want one for chlamydia. They want something that's really sensitive; that's the most important factor. They also like specificity at about 95%. They think fast: 20 minutes is good enough. Cost: According to a clinician, $20 was about

what they thought it should it cost. I will say that when -- there have been limited surveys, focus groups for individuals, and generally, individuals say that they don't really want to spend more than $10 on one of these tests. And then obviously minimizing the amount of equipment that needs to be done, to the point of hopefully no equipment, is something that clinicians would like to have.

WHO also has what's called the ASSURED criteria for point-of-care testing, so again something to think about. For over the counter, WHO wants these tests to be affordable, sensitive, specific, user friendly and simple to perform, rapid and robust, equipment free, and gets delivered to the end users.

There's also some interesting -- one interesting study where they talked about doing e-STD services. Someone's thinking about using the Internet for everything now. So not only could we do e-testing through the Internet, but we also could do e-prescriptions because that's the direction that prescriptions are going in the United States. And actually, New York State has actually legislated that all prescriptions in New York now have to be done electronically, which adds some complexity when you want to add on. Like when we do EPT, we mandate that health education materials go with that prescription, but how do you do that when you're not sure exactly where the partner's going to show up at which pharmacy to collect the medicines? And again, obviously, we want to look at -- there could be some very innovative ways that we could have patients facilitating Internet access for their partners through both e-testing and e-prescriptions.

We have been doing Internet partner services for quite some time. So if any of you guys haven't tried this, you can log on to inSPOT or Don'tSpreadIt, and you can send a little love note e-card from a concerned friend about your health and let someone know that they have been exposed to an STD and you can pick your STD -- this happens to be crabs and scabies -- and hope that the partner goes in and gets evaluated and treated. But

certainly it would be great if we could link these Internet partner services to testing services for the partners as well as treatment.

So bringing me to the end of the discussion, I sort of came up with my own sort of potential benefits of over-the-counter chlamydia and gonorrhea testing, not knowing that the FDA's done a fantastic job kind of looking at pros and cons of testing for the diseases we're talking about today. So I sort of made the assumption that we are going to have a sensitive and specific, easy-to-use and interpret, affordable and acceptable to the intended user test. So that was what I started with. Now, I know that's a big assumption, so we'll have to have those discussions. But obviously if that is the case, we really could increase access to and reach of testing, which then may result in the outcome we want, which is earlier diagnosis and more timely treatment with improved health outcomes and reduction in further transmission.

Certainly, we've heard from patients that they -- even though there's not as much advocacy for the other STDs as there is for HIV, there are a lot of individuals with chlamydia and gonorrhea that are very stigmatized when they have these infections. Certainly, over-the-counter offers that privacy and confidentiality we know patients are looking for. And certainly there's the convenience factor and the fact that women at least seem to prefer collecting their vaginal swabs at home.

So these are the benefits that I see that we really could improve reach and scale and access to testing that we've not been able to do through the healthcare system or through our public health outreach programs.

But there are some risks. And again, these are potential; these are all speculative. We really need to do studies to validate these concerns as well as the benefits. So we could have a risk that the patient may not seek treatment or inform their partners of an exposure to a communicable disease and the need for evaluation and treatment. And we have

known there have been cases of partners coming in and being diagnosed with chlamydia or gonorrhea, making assumptions about where they acquired the infection from, like it wasn't the wife, it was the side partner I had. And actually in some states there are duty to warn laws, and when the wife ended up with a PID and had not been informed that she had been exposed to chlamydia and gonorrhea, the provider ended up in a fairly large lawsuit. This was actually in California.

There's also this concern about unintended users. I call those the older, sexually active worried well. You know, as we age, we know there's a lot of change in partnerships now in our society, and they may be the ones that utilize this over-the-counter more, which may result in more false positives, which has a whole laundry list of challenges.

And then the last concern is if these positive tests are not reported to public health. I think our concern is that really our surveillance systems will be compromised. As I mentioned, our funds could be misaligned. Our public health action intervention -- interventions could be misguided. Certainly, we wouldn't be able to monitor antimicrobial-resistant gonorrhea strains. And we also do a lot of economic modeling and network analysis of transmission dynamics with our surveillance data, and so those analyses may be wrong.

So, in summary, at least I feel we really need further studies to really understand these benefits and risks because most of them are speculative.

I think the acceptability of self-collection and home testing needs to be looked at in a larger and more generalizable population, at least stratified by age, gender, SOGI -- and for those of you who don't know this new term, it stands for sexual orientation and gender identity -- and race, ethnicity, and other cultural factors that could be barriers to self-collection or home testing.

Obviously, the role of public health reporting as a requirement and acceptability

needs to be evaluated because there are some people that do not want to be reported to government. There's a lot of lack of trust in government systems in some segments of our population.

Obviously, the risk and benefit and cost of unintended users with lower prevalence is not known. And obviously, we need some tests. And then also just patient adherence to timely treatment and timely partner management after testing needs to be studied. And I think there could be some innovative ways that we could support testing and partner treatment through over-the-counter tests. But again, we just don't know how many will seek treatment and inform their partners after a positive test.

So with that, thank you very much. I'm happy to take some questions.

(Applause.)

DR. CALIENDO: Thank you, Dr. Bolan. That was a very interesting presentation.

So we're going to open this up for questions, and remind you that if you don't think of anything right now, that we'll be having a larger -- a longer discussion in the afternoon.

So go ahead, Barbara.

DR. VAN DER POL: Barbara Van Der Pol.

Dr. Bolan, you presented really great and interesting data, but there were two pieces, I think, that really go together that weren't necessarily right next to each other in your slide deck. Can you go back to that HEDIS graph? Can you go back?

DR. BOLAN: I think so. Yes.

DR. VAN DER POL: So one of the things that Dr. Bolan mentioned that's really critically important is that our infrastructure and our funding streams -- the HEDIS one, yeah.

DR. BOLAN: Yeah.

DR. VAN DER POL: There you go. Those are going down, and so people are actually

accessing healthcare less, but this HEDIS graph is based on the number of people who engaged in the healthcare system that year. So these are women we had access to and were unable to screen. And so if you consider them, the bigger problem now of losing access to some of those people, these numbers would go even further down, and I think those two pieces in combination raise quite a concern, and I think that's part of the impetus for this type of meeting.

DR. BOLAN: And I would add the closure of STD clinics, too, is another access point that we've had in the past that was much more robust than it is available today.

DR. PORTIS: Natalie Compagni Portis. I'm the Patient Rep.

And I think my comments follow on yours, that when we look at that data and the online HIV studies and the other e-studies that are being done, I think that there's a certain type of patient that is going to be able to access this, they're going to follow through, they're going to fully comply. But I'm concerned that the same underserved population that we always have becomes even more underserved and that we lose even more of those people. And then that goes also to your comments that you brought up about the public health issues, that, you know, often -- well, it's a whole other issue, but industry concerns and what industry wants is not what really is going to benefit the patient and give us the public health data that we really need.

DR. BOLAN: I mean, I will say that one of the advances that I'm seeing is mainly through HIV funding, but we also recognize a lot of STD prevention is HIV prevention. With the new AIDS strategy, there's really new emphasis on (1) dealing with co-occurring conditions. If you don't deal with housing and stability, if you don't deal with mental health, if you don't deal with substance abuse, you're not going to have people stay on their antiretrovirals. So a lot of prevention funding in HIV is being used towards linking to care. So there's a huge movement to link to care that we never really saw in public health before.

I mean, we in STD are always accused of, well, you just take care of the STD and then you never see the patient again and you don't worry about it.

So I think we've got some opportunities to really scale up and get people into care in a broader way that, I think, will help all of our conditions. I find it interesting that I know, early on with the HIV testing debate, there were concerns about counseling, and if people had a positive test, what would they do with it when they're sitting at home? I think it's interesting now that the big emphasis for HIV is this linkage to care and viral suppression. And so they've got the same concerns, that people are just, you know, testing at home and then are not getting into care. Is that benefiting -- you know, it's not benefiting the individual, from what we know now, but what treatment can do --

DR. CALIENDO: So Gaydos and then Hammerschlag. Let's go with Gaydos first, Hammerschlag, then Nolte, then Henrickson.

DR. GAYDOS: Charlotte Gaydos.

Just a point of clarification. We do have data on linkage to care for "I Want the Kit." We actually allow people to get their own results now, trying to simulate what would happen if they did do the test themselves at home, and we follow them for about a year, calling to see if they did get care to the place that they named they were going to get care, and about 80% of them do show up for care.

My question is, Gail, what's your opinion about whether or not education can play a role in reaching out to get to the people to empower themselves to look after their own sexual health? People seem to be very interested now in their own health, as you can see from a lot of Internet searches. We've done a great job in this country of educating women that they need to be screened for mammograms and that they need to have Pap smears. It's taken years, but it has been an effective public health program. Do you think that we can, at one point, educate women and men enough to be empowered to think about their

own sexual health, to actually test themselves, with the recommendation for women, anyway, once a year for chlamydia tests with an over-the-counter test?

DR. BOLAN: Yeah, I'm optimistic based on there was just an evaluation of the GYT program on college campuses, and it actually showed that they had, you know, seen the campaign, heard about the campaign. Not only were they more likely to know about chlamydia and the need for chlamydia testing but they actually went in and got tested. So Mary McFarlane is the senior author on that, and I think that that is just out, so I think it would be great if you can get your data out on the access to care.

DR. HENRICKSON: But that's college campuses, right? I mean, that's not --

DR. BOLAN: Pardon me?

DR. HENRICKSON: There's a lot of women who aren't in college.

DR. BOLAN: Yes, that's true. And that's a lower-risk population. But no, I think -- I think if you follow what adolescents are doing online these days and the amount of online activity just to get information about STDs, access to porn and other things, you know, I think there is opportunity with social media, and also there's a lot of peer groups now that are influencing, you know, LGBT issues in high schools and alternative schools. So I'm an optimist, but I think we have to, you know, do a better job. We need our parents talking to our children, and we need our teachers talking to our children, and we need our providers talking to our children and young adults when they come in to the healthcare system. So it's a multifaceted approach I think we need to take.

DR. HAMMERSCHLAG: I just want to throw maybe a little wrench into this. There's just one concern that I often -- oh, Maggie Hammerschlag, Downstate Medical Center. The point is where the tests get used by populations or in situations where they have not really been evaluated specifically. If it gets used, let's say, in minor children, not even adolescent, if it gets used -- because then you start stumbling into some very important legal

implications in terms of potentials for sexual abuse being used as -- to prove it. I mean, it could be a real can of worms if you do it appropriately, and I've seen that. I've had some situations, for instance, with a point-of-care test. You've heard of the BD Affirm.

DR. BOLAN: Um-hum.

DR. HAMMERSCHLAG: Well, that was used even in a laboratory out of context and ended up in destroying a family. This happened in Oklahoma. So that is just one smaller thing where they're going to have to come up with some kind of disclaimer, but it could have some devastating legal implications.

DR. BOLAN: I think, Charlotte, you went down to 14 for the people that were accessing tests and "I Want the Kit." But I will say this conversation also occurred with expedited partner therapy. And for those of you that don't know what that is, that's where you give extra medication to a patient to take to their partner, if you assess that that patient's not going to come in and get care, and most states had to change the law and bypass the Medical Practice Act so that you could prescribe without a good-faith exam. And so some states actually were concerned about minors giving medication to minors, and it restricted EPT laws down to 16 and not below. So I think that's something obviously, I think, would be great for the Committee to discuss.

DR. HAMMERSCHLAG: Yeah, but I'm thinking of maybe a parent going out and getting the test and using it on a child --

DR. BOLAN: Yeah.

DR. HAMMERSCHLAG: -- let's say an 8-year-old, because they're suspicious that something is going on.

DR. BOLAN: Yes, this is why STDs are always a little messy.

DR. NOLTE: Rick Nolte.

You know, the previous speaker alluded to the fact that we really have no

information about how the impact of an over-the-counter test for HIV, what that has in sort of the broader public health perspective. But I wonder whether we haven't already done the experiment because, I mean, there's been over-the-counter tests for HIV for how many years now, and where we are now in terms of a public health perspective is doing wider-based screening for HIV using point-of-care tests or in-laboratory tests. So after going through all of the -- I mean, it's a shame that we don't have that data.

DR. BOLAN: Yeah, I actually tried to -- because the Division of HIV is a different division than my division, I tried to do some, you know, exploration. Were they evaluating the impact? You know, who is getting tested at home? Do they show up for confirmatory tests somewhere? Do they come into care? A lot of us do ask, when people come in for STD testing -- I know it's traditionally asked in STD clinics -- why are you seeking testing? And I have to say, at least anecdotally, I've not heard a lot of people coming in and saying because I did a home -- an online test. It's usually my partner told me I should come in and get checked, I think I'm at risk, I need to get tested, things like that. And also I think you guys, in the Executive Summary, mentioned that only 170,000 HIV tests have been done over the counter since it's been licensed.

(Off microphone comment.)

DR. BOLAN: Pardon me? That's one manufacturer, okay. But again, that whole issue of scale and who's getting tested, is it the right people that are getting tested, because I think we do have a concern that our most vulnerable populations are the ones with STDs, and are they the ones that are going to be able to access and afford, you know, over-the-counter testing?

DR. HENRICKSON: But I put to you -- Kelly Henrickson -- I put to you that you can't compare HIV to this.

DR. BOLAN: No, no, no. I agree, I agree.

DR. HENRICKSON: And I mean, HIV kills you. HIV needs doctor intervention to treat. And I guess, out of line, my question was a lot of doctors are going to treat -- could treat these over-the-counter tests without ever seeing the patients. They could just get called, and someone calls in and says hey, I have GC. You know, I'm not coming in. Are you going to give me -- you know, you either give me something or -- you know, I mean, there's a risk here because it's not -- I think there's a risk of patients being treated. Like you said, we treat partners right now without seeing them, okay?

DR. BOLAN: Right.

DR. HENRICKSON: And so will this -- will over-the-counter lead to people being treated without ever being seen?

DR. BOLAN: Right. And then there's missed opportunities for the testing that should be done on other things. But no, I agree, it's not the same as HIV. And I do think, having been an AIDS doctor in San Francisco, you know, there is a need for people that just really want to have that first test at home, and you know, they're not going to get tested any other way. You could make the argument that maybe there are some people with STDs, you know, that are not accessing care. This is the only way that they could be tested, through over-the-counter options, and then we would have to find a way to get them linked to care and treatment. We just don't know. We don't know if the people who would access over-the-counter also have primary care doctors or are regularly into care. There are just a lot of unknowns.

DR. HENRICKSON: Right.

MR. KIMES: Yeah, just a quick --

MR. SIMON: Tom -- oh, I'm sorry.

MR. KIMES: Yeah, just a quick question, maybe a little bit off the path of what we're talking about. You had mentioned that pharyngeal swabs have done fairly well. Is that in

the test environment of nucleic acid testing or the more general IVD side or --

DR. BOLAN: No, it's nucleic acid amplification testing. It's -- you know, we just tell patients to go in the bathroom, and we give them little pictures and tell them to go to the back of the throat and kind of gag yourself and put it into the cup. But the other interesting thing is John Papp, who works in our lab at CDC -- and Barbie, you may know about this -- he's actually got a swish-and-swallow, some kind of a rinse that he's been looking into that might work for chlamydia and gonorrhea NAAT testing. I have not seen the data.

(Off microphone comment.)

DR. BOLAN: The gargle.

UNIDENTIFIED SPEAKER: Swish and -- yeah.

DR. BOLAN: Yeah.

DR. VAN DER POL: Yeah, the gargle and swish was developed in Japan, and they're quite happy with it for NAATs, and so they've been using it a lot. And along those lines, I don't know if it's worth mentioning, but there is a consortium made up of four or five academic centers and five industry sponsors who are in the process of getting a large-scale clinical trial out to evaluate all five of these diagnostic assays for oropharyngeal and rectal samples. So, you know, within the next year or so, we should start having claims, but all of that will be submitted through the regular process, and so that will all get reviewed. But I think that will also give us some things. But then as newer tests come out, we have something that's already approved that we can compare it to. So I think it's a good first step. Yeah.

And I just wanted to add one thing about -- you know, your concerns about is the right population using it or, you know, about infrastructure and who's seeking care. I think we need to keep in mind that the POC tests are going to be an addition on top of the status quo. The status quo may be going away because of funding issues, and so we're trying to fill

in that gap before it gets here. But assuming that the status quo stays fairly similar, these tests are intended to bring us more people. And so if we bring in more people to the testing arena and making testing normative for more people, some of those people, when they get a positive, it will be a cue for them to seek care and they can get tested. So it's a gained opportunity, if you will. Some of those people may not. They may just try to get a prescription through whatever means. But those people who weren't accessing care anyway and did this point-of-care, if they do get treated, it's still a benefit from a public health perspective. It's harder to measure from surveillance, but you know, so there's a real balance here.

DR. HENRICKSON: That's true. Kelly Henrickson. But you'll find a lot of adolescents simply rummaging through their parents' closets looking for any antibiotic to take and give it to their friends, without any seeking of healthcare.

DR. VAN DER POL: Sure. But if these girls weren't going to seek healthcare anyway, we've not lost. We've not gained, but we've not lost.

DR. HENRICKSON: Well, you have them taking weird antibiotics that are probably inappropriate and may cause resistance.

DR. VAN DER POL: Yeah, but they probably were going to do that anyway --

DR. CALIENDO: Okay, okay. You need to remember to introduce yourself before you speak. And poor Tom has been waiting patiently to make a comment.

MR. SIMON: I think I've forgotten.

(Laughter.)

MR. SIMON: If I understand correctly, notwithstanding the problems that come with OTC tests, at-risk populations, uneducated populations, underserved populations, racial, ethnic, minority populations, taking those into consideration, if very few, I mean very few take advantage of the OTC tests, what is the major harm with having OTC tests available to

those populations? If they're not going to be tested anyway, if they're not going to see the doctor, from the information we have now, what is the harm, other than -- I realize there is harm, if you will, with the examples that have been given. But if it's asymptomatic and you're not going anyway, why not?

DR. MARTENS: Well, to answer or ask the question I was going to bring up, the two biggest harms I see are -- and one's the emotional harm. I think it's going to be very difficult to get a test that has a very good sensitivity and specificity. So in low-prevalence populations, you'll have a lot of false positives, a lot meaning 50, 60, 70%. So as a clinician that sees -- maybe 10, 20% of my practice is explaining to people, no, this is a screening test. It does not necessarily mean you're positive. But that's emotional. Then I worry about mostly what Kelly was saying is that I get reminded every week that I'm in the clinic with the residents, when they trick me and they say what's that? And I look at that and say I know, it's herpes. And they go, yeah, it's herpes, but it's also syphilis and something else.

So they're going to be tested and even positive for gonorrhea and chlamydia, and you -- but you know that 50% of people with one STD have another STD, and they're going to focus on that one STD, and they're going to treat it, and half us are going to give them a prescription over the counter. I'd like to see them say you must have a follow-up appointment. You know, how many will come, I don't know. And Barbara's right. Even if we get half of them, it's great. But we've got to get that through the mentality. We found one. We got to say there may be more, and then they've got to see somebody to do testing. It's not going to be available over the counter.

MR. SIMON: I believe you're correct on that, but I think there was a slide that showed 42 to 65%. What was that slide?

(Off microphone comment.)

MR. SIMON: Oh, this is Tom Simon. Sorry. I think it's the next slide, I believe. No,

the other way maybe. But I thought it was 42 to 65%.

DR. CALIENDO: The numbers that returned a kit from Dr. Gaydos's study.

DR. BOLAN: Yeah. Yeah, yeah, yeah.

DR. MARTENS: Yeah. This is Mark Martens.

What was the positivity rate, Charlotte, in your study?

DR. GAYDOS: It's increased over the years. It's an average of about 65 to 75% now.

MR. SIMON: Of positive results?

DR. GAYDOS: Huh?

UNIDENTIFIED SPEAKER: Of return rates.

DR. GAYDOS: Oh, no, return rates.

DR. MARTENS: This is Mark Martens.

What's the percentage of positive results --

DR. GAYDOS: Oh, the percent of runs. Originally it started out around 10% for chlamydia for women. It's now running around 7 or 8%. We're only active in the state of Maryland and the District of Columbia, so you know, it's low numbers. It's not a nationwide program. Yeah. So averaging, depending on whether it's female or male and depending upon whether it's a rectal or a genital sample, our genital samples on males is running around 75% right now. But the prevalence of chlamydia is running around 7 or 8%. It's about 1% for gonorrhea in women and about 4% in men. And for gonorrhea, we also test for *Trichomonas,* and that's running right around 8 to 10% for women and around 7 or 8% for men. So it depends on the sample, the sex, and the sample type.

MR. SIMON: Tom Simon.

Is that positive results?

DR. GAYDOS: Um-hum.

MR. SIMON: If that's the case then --

DR. GAYDOS: Yeah. So it's a gain-gain. You know, some of these people we also -- the kit also sends them an e-mail if they're positive, or a text at 3 months, saying it's time for your repeat sample. And if they go online and get their own results, then it gives next steps. You must go to a clinic that you selected to get treated, and you should get treated again or should get sampled again in 3 months. The website also sends them a text or an e-mail automatically to say that the results are ready.

So we have recently offered two types of home tests. Last year we offered, and just published, ahead of print, in *Sexual Health*, the ability for a woman to do her own *Trichomonas* test at home and go back online and say my picture looks like this, or my lateral flow; I interpret it as -- and then a whole bunch of questions about acceptability and feasibility and whether they would recommend it to a friend, whether they would buy it over the counter if it were available, a lot of good acceptability and feasibility information. So that study is over. That was a consent study, and it was compared to the actual NAAT test that was mailed in.

And currently we are offering a home HIV test, and we have about 70 people who have ordered the test, gone back on, interpreted their results and answered a questionnaire about whether they believed their results, whether or not they'd recommend it to a friend, and how much would they pay if they could buy it over the counter, and they really only want to pay $10 or $20 for both of those tests. About the cost of a home pregnancy test.

DR. CALIENDO: Okay, let me just interrupt.

DR. GAYDOS: But acceptable.

DR. CALIENDO: What I want to focus on is if we have any clarifying questions for Dr. Bolan, because we're going to have plenty of time this afternoon for discussion. This is a great discussion, but I want to make sure we get to clarifying questions.

So go ahead, Cathy.

DR. PETTI: Hi, this is Cathy Petti.

Since we're in this era of great uncertainty in the analytical performance of the tests, and also great uncertainty on how these tests would be received by the healthcare system and being integrated in the healthcare system, I would very much like to know Dr. Bolan's position. If this test would be a first-phase approach requiring confirmatory testing, would the position of the CDC change if confirmatory testing would be a requirement rather than it being a standalone diagnostic test?

DR. BOLAN: Certainly, we haven't discussed that at CDC. I know that we went through this early on with NAAT testing, and there was a feeling that labs had to do confirmatory testing that ended up -- Kaiser actually did a very nice study showing it was, you know, completely unnecessary and very costly. You know, I'll just give you my personal assessment. You know, from the way that these tests have been performing, you know, I think it would -- you know, I'm not sure what a confirmatory test really would do. I don't know. You know, I would -- what Barbie and Charlotte think, but to me that doesn't feel like -- I mean, our tests are pretty good. Our challenge is that we don't have them cleared for the sites that we need to detect, and we don't have them cleared for self-collection. So I think if a test -- a NAAT test is positive on an over-the-counter test that is performing like a self-collected NAAT is now, that that wouldn't need to be confirmed.

DR. VAN DER POL: I think the concern is going to be the confusion that physicians will have when dealing with a patient coming in and saying I got this test off the Internet; will you treat me? Because we don't know what's happening with those Internet-based tests because an OTC test that was approved by the FDA, you know, you could just -- in the kit, it could have a card that said the name of the test is this. The sensitivity and specificity, negative and positive predictive value according to our package insert is this. I tested positive for it, and they tick chlamydia or gonorrhea and then give that card to their

provider, simple solutions so the provider has some confidence. But with the Internet-based stuff, that's a whole other ball of wax. So I think the OTC will actually be more regulated and more standardized and enable better patient care without repeat testing. But you should be tested for other pathogens, right? That's that opportunity.

DR. CALIENDO: This is Angie Caliendo.

I think your point is interesting, though, the other pathogens. So I think one of the things we're going to have to talk about this afternoon is how we're going to educate clinicians when the patient calls with this result. There are going to be docs who will just want to treat over the phone and be done with it, and there are going to be other physicians that say, wow, you know what, I need to bring you back in. Have we now defeated the purpose of the over-the-counter test? Because if they were going to access healthcare, they already would have. And so it gets complicated. How are we going to get the subsequent STI testing completed? How are we going to educate physicians on what to do with these results?

DR. BOLAN: I agree. For people who are in care and have a provider, that's a different population than, say, someone who doesn't, and maybe the screen over the counter could be a gateway to getting them into healthcare.

DR. CALIENDO: Right. But still, now I'm a primary care doc, and I've never seen you. There's no way I'm treating you for GC or chlamydia over the phone without having ever seen you, right?

DR. BOLAN: Absolutely, because you're breaking your medical practice.

DR. CALIENDO: So what are we going to do? Into STD clinics maybe? The other question I had for you is do we have any insight at all or data on who is actually doing over-the-counter STD testing right now? Is it the worried well or is it high-risk people? Do we have any sense of that?

DR. BOLAN: We have health department staff we call secret shoppers, and they will go into an STD clinic and see if, you know, the clinic is adolescent friendly. Are they requiring parental consent to get services? They just kind of pretend. So we also have secret shoppers that call up places. So we have tried to get information from these online testing sites about what information do you collect, how do I get treated, am I reported to the health department?

The National Chlamydia Coalition did an assessment about 10 years ago and a guide and they called one of the companies. They actually said to him, "Oh, we don't talk to the STD Gestapo." I'm not kidding; that was the quote.

The online stuff is not regulated, as far as I know. Some of them don't even have certified labs. And I know that, Charlotte, there was one study you did where you actually spiked specimens, ordered the test online, spiked it and sent it back and got negative results. So we at CDC do monitor, you know, new tests on the market. When the new syphilis test came out, the rapid syphilis test came out, the first generation, we bought kits, and we will look at them at CDC. So we don't have a lot of resources for reference lab work, but we're still trying to maintain that work. And I would anticipate that if there are over-the-counter tests, we would be doing our reference due diligence to be periodically, you know, buying the kits ourselves and spiking them and sending them back and see what the results are.

DR. CALIENDO: Okay, thank you. I want to thank Dr. Bolan for her presentation.

We're going to take a 10-minute break right now. I need to remind the Panel members to please not discuss the meeting topic during the break amongst yourselves or with any members of the audience. We'll resume at 10:30.

Thank you.

(Off the record at 10:20 a.m.)

(On the record at 10:40 a.m.)

DR. CALIENDO: Okay, can you please take your seats? We're going to resume the meeting. So a couple of announcements. One, for the record, Joanna Cain will not be attending. She was unable to make it due to weather. And just a reminder to everybody, when you speak, to please introduce yourselves.

And we're now going to hear a presentation from Dr. Stephen Lindstrom. At the conclusion of the presentation, we're going to have a period of questions, as we had for the previous two speakers.

So, Dr. Lindstrom.

DR. LINDSTROM: Thank you very much. So my name is Stephen Lindstrom. I'm the Team Leader for the Diagnostic Development Team at the Influenza Division of the Centers for Disease Control, and today --

DR. CALIENDO: Can you speak a little louder?

DR. LINDSTROM: Louder? Sure. It's not often I hear that. This is on, right? Okay. And so today I'll be discussing the public health perspective on the potential benefits and risks of over-the-counter influenza diagnostics.

A brief overview of the discussions today. First, I'd like to go over the burden of disease and demonstrating the estimated burden based on diagnostic test results; and then looking at the treatment of influenza, specifically CDC guidance versus actual practice at clinics and hospitals with use of antivirals; and then discussing the role of diagnostic tests and focusing more so on the rapid influenza diagnostic tests, the rapid tests that are used at clinics and at point of care, and their pros and cons and limitations, and efforts made for improving diagnostic testing in these arenas; and lastly, to discuss the potential benefits and risks of over-the-counter influenza diagnostic tests.

So with the burden of disease, influenza, there is an average of greater than 200,000

influenza-related hospitalizations per year in the U.S., and this is estimated on modeling studies over several years. Efforts are focusing on higher-risk groups of children. We have higher rates in younger children of less than 2 years as well as less than 5. And then the adults, the highest rates of hospitalization are in the greater than 65 years and those with chronic illness.

If you look at the seasonal influenza-associated mortality in the U.S., there's an estimated -- average severity is variable, and it can range anywhere from 3,000, around 3,000 to 48,000, depending on the severity of the year, and this is based on years up until 2007. Again, we see the highest mortality in persons of greater than 65 years and those with chronic illnesses, of pulmonary and cardiac disease.

Mortality data is limited for children, but it has become a reportable result, and so we do have estimates. The estimated average is approximately 92 reported influenza-related deaths amongst children aged less than 5 years. Over the last 2 years, we had 148 reported last year, as well as this year we've had 85 thus far this year in 2015 and '16.

This is an example of the types of data we collect for surveillance purposes. These are data that are shared with U.S. CDC with the clinical laboratories, and so these are typically influenza A and B results. So these are the data that are reported to our systems and that we use to understand relative burden and seasonality influenza for each year. From those, we get a subset that is sent into public health laboratories in the United States, where they are able to perform additional characterizations that involve influenza A subtyping and influenza B genotyping. That gives us a much better understanding of what the relative burden of the illness is in the U.S. by subtype or genotype and by season. If we look at season-by-season data, this is influenza detection by season over top of each other so we see each season. What this shows is that even though there's a similar seasonality from year to year, it is not always the same, and that depends on what viruses may be

circulating, whether it's an influenza AH3 versus influenza B or pandemic H1. And so we do see a different range of seasonality and different peaks of -- different timing of the peak of a prevalence in the population. And this becomes important, as was mentioned earlier, with the predictive values of tests, whether flu is actually circulating in a particular community and what impact that would have on the performance of a test with predictive values.

This just demonstrates, by year on year, the variability of the prevalence of different viruses and their associated burden. So the burden of flu can be due to either an H3N2, for example, in 2013 and '15 or, for example, H1N1 in 2014. In the green at the bottom there, you can see the similar seasonality of influenza B, and that can be between B Victoria and B Yamagata lineages. Now, this data is important also, not just for understanding burden but for understanding the prediction of vaccines and understanding the effectiveness of vaccines due to the relative prevalence of the subtype or the component viruses of that vaccine.

If we look year on year, this is the prevalence of cases, so the total number of cases reported annually. You can see year on year. Most cases are reported in the middle there, in the middle-aged groups, 18 to 49, 50 to 64. However, you can see there on the bottom chart, it shows the hospitalization and the clinical burden, with greater than 65 bearing the brunt of that effect. So it just demonstrates that the burden isn't always in the highest prevalence age group.

This is a graphic demonstrating the estimation of influenza disease burden and how they're calculated. I share this because it is a cumulative dataset that there are assumptions and models associated with it. And so there are algorithms applied to reported numbers and assumptions made, and the key assumption at the beginning of this graphic is that we're looking at reported rates of hospitalization and reported confirmed

cases. So the role of diagnostics in actually estimating all of our burden plays a direct role. And if we're misdiagnosing, then we're really under -- we're over-representing the burden of a disease.

So looking at the forms of treatment -- and specifically, this is the antivirals, the neuraminidase inhibitors -- the CDC antiviral recommendations that have been made is that all patients in the following categories with suspected or confirmed influenza should be treated as soon as possible, without waiting for confirmatory influenza testing. So this includes hospitalized patients, patients with severe or complicated or progressive illness, and patients at high risk of complications, as I mentioned earlier. This should not be -- so treatment should not be based on diagnostic testing or tests results per se.

So the persons at highest risk include, as I mentioned, children under 2, adults greater than 65, pregnant or postpartum women, American Indians, Alaskan natives, persons with morbidity, long-term care facility residents, as well as persons with underlying medical conditions and particularly those that are immunosuppressed.

Now, with detection of influenza, it's critical that people present early, and tests are conducted within the first 2 days of onset. And so this is a study that looked at the presentation of individuals, and this particular plot shows the -- or graph shows the high-risk populations, and they're reporting timeliness for care, and we can see that amongst all of these high-risk groups, it's about 25 to 30%, in that range, within -- that are reporting within the first 2 days of onset, which limits sometimes the ability to detect the cases if they present too late on illness. And it won't go forward. There we go.

This shows the proportion of outpatients with acute respiratory illness that were prescribed influenza antiviral medications in the 2013-14 season. And this particular graphic separates the populations from -- by severity or risk, and that these populations -- we have those all high-risk groups as well as the less than 2-year-olds, greater than 65, and

those with any other medical conditions. And we can see that they had very low prescriptions for antiviral medications, from 15 -- actually 6% for less than 2-year-olds and only 17 for those over 65 years old.

If we look at a study that evaluated outpatients with acute respiratory illness and their treatments, we found that all patients -- only 8% overall were prescribed an antiviral, whereas 34% were prescribed an antibiotic. High-risk patients, only 10% were prescribed antivirals while 35% were treated with antibiotics as well. And for those that we were trying to get in within 2 days of onset, even then only 19% were treated with antivirals, with much higher prescriptions for antibiotics.

So in this study from the 2013-14 season, fewer than half of influenza-infected high-risk outpatients that were seeking care for acute respiratory illness that presented early enough for optimal neuraminidase inhibitor were treated. Among high-risk patients who presented early, only 15 were prescribed antivirals. Amongst those high-risk patients who presented early and who had laboratory-confirmed flu, 43%, or who presented during peak season, only 31% were treated with antivirals. And so at the influenza season's peak, 42% of high-risk patients who presented early and had laboratory-confirmed influenza did not receive antiviral treatment.

So in a second -- in another report by Rolfes and others, they looked at the respiratory viral testing and influenza antiviral prescriptions during hospitalization for acute respiratory illnesses. What they found -- and this is looking at the factors that would encourage prescription of antivirals. Almost always these were test-directed therapies and only the positives that were primarily the cause of antiviral prescriptions, and a very low percentage of providers provided empiric therapy without depending on the diagnostic test result. So the providers had a very high dependence on test results. That led to low rates of empiric description. Only 3.4% of inpatients were ordered an antiviral prescription

empirically, and this suggests that opportunities for influenza treatment are missed and that healthcare providers are encouraged to start antiviral treatment, as per CDC guidance, as soon as possible for patients hospitalized with suspected influenza and especially during periods of high influenza-circulating seasons.

Also during the 2012-13 season, antiviral medications were under-prescribed and antibiotics may have been inappropriately prescribed to a large proportion of outpatients with influenza. So we're finding that continuing education on appropriate antibiotic and antiviral use is essential to improve healthcare. Few ambulatory care providers appear to follow current antiviral guidance, and additional efforts are needed to understand the barriers for use of antiviral treatments, especially in ambulatory care settings and high-risk populations.

Looking at diagnostic tests and their roles, this is just showing the different diagnostic testing approaches for influenza and from rapid influenza tests, on the left there, to higher complex PCR tests for public health laboratories, reference laboratories. And along that same continuum, you could add performance for sensitivity and specificity, where those on the right would have higher performance with regard to sensitivity and specificity, while RIDTs would be on the other end of that spectrum with lower performance; however, with our RIDTs and DFA, quicker turnaround, and the slower turnaround for PCR. So there is diagnostic value with regards to time to result.

But this is a study that was performed by Millman, who looked at the use of different diagnostic methods in the FluSurv-NET, a provider and hospital surveillance network, and what they found was over a period of approximately 10 years starting in 2003, that the usage of these different technologies did change, but it was very sudden. Prior to 2009, most providers were relying very heavily on rapid tests. There was also DFA fluorescence antibodies as well as culture that were used in many of these hospitals. And starting in

2009, a lot of the providers gave up their culture systems and moved towards molecular. And so you can see that big spike in molecular testing there, although the rapid tests are continuing to be used.

The one thing he did find also -- this is a review of literature. This is not an actual clinical evaluation or prospective study on the performance but a review of literature that reported on different parameters of these tests. But what they found was the performance of real-time RT-PCR or RT-PCR in general, those NAAT tests performed fairly similarly, at the top of the table there, with between approximately 80 to 100% in all age groups. But when you looked at rapid tests, when you got out of that younger age group, the performance tended to suffer, and particularly in our highest risk group of greater than 65, it was less than 50% and almost as low as 8%.

In a separate study which is not published, but it had two surveys, one in 2006 and one in 2012 and '13, looking at the different laboratories in the FluSurv-NET, and again, the same providers, you can see that molecular assays, the second from the left there, there was a spike, as we showed, from 10 to 63, so approximately 30%. But on the very far left is the usage of rapid tests, so there's still a very high, even increased dependence on rapid tests in 2013. So people, the laboratories and the hospitals have not moved away from their dependence on rapid tests. Instead, they continue to be maintained.

So focusing on the rapid test, because this is where we're looking at the point of care and those tests that are predominantly used in that arena, this technology -- most of these kits and tests are monoclonal antibody tests that targets the nucleoprotein of the influenza virus. As I mentioned, the results can be obtained within about approximately 15 minutes and are available to clinicians during the time of a patient's office or clinic visit. So these are point-of-care tests that are used quite frequently. Unfortunately, their performance is extremely variable, and often suboptimal sensitivities have been reported in previous years.

Meta-analyses of several studies have looked at -- and particularly, the sensitivity of these tests is quite low, and the sensitivity can be even considered lower when the comparator is moved from cell culture to molecular tests that have a higher sensitivity; the limitation of these antibody tests is even more pronounced. And as I mentioned, with the elderly especially, we have lower sensitivity in adults than in children.

So what can be done to improve this situation? There are several things we can look at. One is just looking at the devices themselves. So how do we improve the tests, whether it's improved antibodies, methods, readers, detection systems, better guidance for clinicians? And at the point of care, we look at the quality and timing of specimen collection, making sure they're collected in a timely manner when shedding a virus is the highest; use of local flu data to improve predictive values, so understanding how much flu is in your neighborhood or your community to understand what the predictive values should be or would be for that particular test. And then looking for tools for manufacturers, the clinicians, and regulators, and trying to look at evaluation standards and other diagnostic tools.

So in 2010, there was a public health initiative to improve these patient diagnoses, and the goal there was to improve the use of rapid tests for clinical management and public health practice. And so they split these into three general areas, for better practices, better guidance, and better tests. And as I mentioned, for better practices we want to facilitate optimal use. Better guidance was dissemination of relevant information for clinicians and laboratories on the limitations of these tests. And better tests to be generated, to be made available to clinicians: One is to identify factors that can lead to improved rapid tests, and the other, to provide incentives to manufacturers and others, through CDC and BARDA, FDA and professional societies, to actually generate and manufacture and qualify better tests in the arena.

Something that's been specific to influenza rapid tests, working with FDA and CDC, is that there were inputs to have a new device regulation or a proposed regulation, through FDA, to reclassify rapid tests from Class I to a Class II device with special controls, and this came out of a 2013 public meeting from the Microbiology Devices Panel. And what this will do, the goal of this is to enable FDA to enforce higher performance criteria and monitoring of annual reactivity testing and analytical performance validation by manufacturers of influenza virus antigen detection systems to try to improve these tests that are out there and being used so often.

So what our responsibility is, then, is to provide those mechanisms to enable the annual postmarket evaluation of these tests: providing viral panels of characterized virus reference standards; enable the annual performance monitoring against seasonal influenza to make sure that these tests are able to continually detect influenza as it continues to evolve; as well as evaluating against emerging novel influenza viruses so that we understand their reactivity when there's a suspect avian, swine, or other non-human influenza case, and being able to predict what the expected result might be against those non-human influenza viruses.

This would also enable or encourage heightened performance by establishing minimum performance criteria so industry understands what the expectations are; it's not establishing performance to a predicate but to another standard because those predicates are quite old and basically are set off of cell culture standards instead of higher standards that are more established and continuous across the industry. And also looking to introduce, as I mentioned, the advancing technologies, to encourage manufacturers to develop new methods, techniques, technologies, and making informed decisions regarding the patient management.

So looking at the situation with rapid tests and how that then translates into the

benefits and risks for over-the-counter tests, because that is the current technology we're dealing with right now, point of care -- so looking at the benefits of OTC flu tests, as mentioned, the earlier we can test, the earlier we can initiate treatment. And so this is a potential benefit for patients seeking earlier treatment, especially our high-risk populations. And also if they are using test-directed prescriptions, it would also enable or hopefully facilitate lower prescription of antibiotics.

Home testing may also decrease, as I mentioned earlier, the healthcare visits for worried well with negative results, lower-risk patients with positive results that may not seek medical care, or those who want to self-quarantine and reduce community spread through the workplace and/or schools. And this is all, as I mentioned earlier, assuming OTC tests with high sensitivity and high specificity.

As mentioned earlier also, this could be used as an opportunity for improved education, for example, encourage follow-up care, follow-up testing, medical attention, or direct prescription for the physicians.

There's also the potential for improved surveillance data. So as I mentioned earlier on that slide, the data that we collect to understand burden in the community comes from the clinics and the hospitals. This would add another dataset to understand, if the results are reported, to understand the potential improved -- sorry, understand -- another dataset for understanding the surveillance of influenza in public health.

However, as mentioned earlier, again, the primary risks to this are the inaccurate results, as we see with point-of-care tests, for false negatives or false positives. There's also the risk of respiratory specimen collection with regard to variability of specimen collection, as I mentioned earlier, by laypeople, as well as the safety considerations for collecting -- self-sampling your respiratory specimens, your NP swabs or what have you.

As I mentioned, there is also the reporting of results. So if people are self-testing,

what happens to those results? Whether they be positive or negative, are they being reported into public health systems? And what requirements could be put in place for development of these tests to hopefully put in systems, to enable perhaps electronic reporting systems or other systems where these data will be entered into the public health datasets? And then I'll just leave the impact on patient treatment and management. Are these people actually going to get treated if they're positive?

With false negative results, as now with point-of-care tests, there's a potential for loss -- a potential loss of treatment benefit, and we already see that with point-of-care tests and untreated influenza. And we would also have the risk of increased community spread, where people won't self-quarantine with a false negative and underestimation of burden. False positive results obviously will give you unnecessary antiviral medications, and patients may not then seek treatment for the true cause of illness if they are assuming it's influenza and not another cause of illness.

This could lead to less testing in healthcare facilities, if follow-up or confirmatory testing is not required for these tests, which would lead to less specimens and materials available to public health labs and CDC for doing actual virus surveillance and vaccine strain surveillance where we're looking for antigen variability among circulating viruses. This may give us fewer opportunities to understand the virus characteristics in the community or a population.

We would also have missing data on prevalence of influenza-like illnesses, which is currently a collection that we do have in the influenza surveillance, where we have visits to hospitals as well as outpatient visits as one of our measures of influenza burden for ILI. We also have -- if a poor positive predictive value when flu is low, we will have patients who test when influenza is not active, and that increases the potential of false positive results. And we do see this in the summertime when people do report to public health labs, as we

do obviously see with point-of-care tests, where we do see a higher rate of false positives reported.

We also have the potential for inaccurate test results if the flu viruses change, and so that's where we're looking at postmarket evaluations of these tests as well as -- so one of these risks to avoid -- excuse me. One strategy to try to avoid the future potential of underperforming tests, as over-the-counter arena, is to perhaps apply what has already been considered to address for reclassification of point-of-care tests, to also apply those same requirements to potential development of over-the-counter tests. That would involve standard reference methods prior to testing and clearance and submission, by demonstrating performance data as well as including annual performance monitoring against influenza seasonally and, if necessary, against emerging novel influenza viruses as they emerge in humans.

This is my last slide for this, also looking at some additional questions for consideration for the Panel. So there is the performance of highly performing tests, or basically the need. If they're going to be in a house for over-the-counter use, the highest requirement is that these tests have to be highly performing tests to mitigate these risks to your false positives and negatives, given that they're not going to have any other consultation or opinions typically, unless it's guided to the people in the package inserts. The question of reporting, by having the requirement for communication of results with clinicians, necessary for proper patient management or reporting mechanisms for tests into public health surveillance systems. Challenges remain, as I mentioned, for the rapid tests. So those same challenges we're facing right now also would apply to any pathogen detection system for use for over-the-counter testing for influenza that still need to be resolved. And other considerations, as mentioned earlier, are also ease of use and cost.

So with that, I'll take questions. Thank you.

DR. CALIENDO: Thank you, Dr. Lindstrom, for your presentation.

(Applause.)

DR. CALIENDO: Okay, does anyone on the Panel have any brief clarifying questions for Dr. Lindstrom? Remember, we're going to have an opportunity to question all of the speakers in the afternoon.

MR. KIMES: Yeah, hi. Dave Kimes.

I'm just curious. For the performance of the rapid test, has there been -- are you aware of any identification as to what's driving that? Is it the PIVD? Is it the sampling? You know, do we know what the drivers are?

DR. LINDSTROM: I'm sorry, could you clarify which --

MR. KIMES: The poor sensitivity of the rapid test.

DR. LINDSTROM: Poor sensitivity?

MR. KIMES: Yeah.

DR. LINDSTROM: So I think there are different factors. Well, first of all, there's different market placement by different tests. So we can't say it's one test or another test because some tests always will perform better than others. They are all generally lateral flow immunoassay tests with sometimes the same antibody or multiple antibody cocktail. So in theory, they should all perform similarly, but in practice, they don't. But what we're finding is the difference is -- and this is another reason for the reclassification -- is that they were originally cleared on viral culture as their standard, and viral culture, as your positive and negative result, has high variability in whatever lab you're using for your clinical study, and that can give you an artificially high rate of sensitivity that gets you clearance because you're using cell culture in a lab that does poor cell culture or very good cell culture. And so now, by looking at the performance of these tests against other assays that have been cleared for NAAT tests, real-time PCR or end-point PCR tests, they're finding that, you know,

the molecular tests are much better, and when you use those as your comparator, your performance in these evaluations drop significantly.

DR. CALIENDO: So Angie Caliendo.

So have you seen any evidence that these new reclassifications of the rapid antigen tests have improved their performance? Or was everybody grandfathered in? I can't remember how this worked.

DR. LINDSTROM: The reclassification is pending.

DR. CALIENDO: Is pending. So it hasn't happened yet.

DR. LINDSTROM: I'll defer to FDA on the pending status of the reclassification.

DR. CALIENDO: Okay.

DR. HENRICKSON: I can give the Committee more information later. We had a BARDA contract to do all the testing for all of the FDA-cleared rapid tests, and we did all the analytical testing in my laboratory, and so we have all of that data. I can share it.

DR. CALIENDO: Okay, great. We can talk about it this afternoon.

DR. HENRICKSON: I can share it with you.

DR. CALIENDO: Good. Okay, great.

Go ahead, Rick.

DR. NOLTE: Rick Nolte.

Does the paradigm shift? I mean, the rapid -- point-of-care rapid diagnostic tests for influenza now include nucleic acid amplification tests, and at least some of them give a laboratory quality result in 20 minutes in a CLIA-waived format. So the whole future of lateral flow immunoassays, in terms of rapid detection strategies for influenza, I think, is maybe limited, and does that change your thinking about over the counter versus point of care with respect to influenza diagnostics?

DR. LINDSTROM: Correct. I think what you're -- and what you're referring to, I think,

is the improvement of the point-of-care tests that have been able to adopt some simplified molecular tests that are either automated or the chemistry is especially for reverse transcriptase because influenza is an RNA virus, and it's difficult to test, more so than a DNA target just because of the enzymology. Those improvements have been made at that point-of-care level, and the reason why I'm focusing currently on the antigen-based test is because of simplicity of the test, and if we're looking at a home test, we're not going to be able to take those current molecular tests that are at the point of care and put those into someone's kitchen at an affordable cost price.

DR. NOLTE: I'm not sure about that. I mean, I think that's -- I think there's technology out there that may be almost as simple and as affordable as a lateral flow immunoassay that's based on nucleic acid detection rather than antigen detection.

DR. LINDSTROM: It could be in the future. And I think that's kind of what the ambition is, to develop some of these technologies and perhaps even just move completely away from antibody-based testing technologies and move towards simplified technologies with -- and cheaper technologies for nucleic acid-based tests. And again, as perhaps other pathogens are developed within the field, cheap nucleic acid detection tests for tuberculosis or other things where we've seen that there have been some development of the technologies in that arena, that they could then be applied for other RNA viruses. But then they would also have to go through the qualification for over-the-counter, and we haven't seen those come up in the point-of-care arena yet, however. So that's where, if it's not in the point-of-care region of qualification and performance evaluation, it's a very large hurdle to get to the over the counter.

DR. CALIENDO: I have Maureen and then --

DR. BEANAN: Maureen Beanan.

So I just have a question related to estimating the influenza disease burden.

DR. LINDSTROM: Um-hum.

DR. BEANAN: Since it's based on hospitalizations, having the over-the-counter tests won't impact durability to make that calculation, correct?

DR. LINDSTROM: It depends on what your measure is. There's hospitalizations. One of those measures is hospitalizations as a measure. There's death. There's also ILI and there's confirmed ILI. So it depends on what dataset you're actually looking at. The datasets that I presented there were on hospitalizations of laboratory confirmed, and so they depended on that technology a lot. But then again, those laboratories and confirmations in the clinics and the hospitals a lot of times were point-of-care tests, rapid tests. And so because of their limitations on sensitivity in the elderly, they estimated that they were underestimating burden in the elderly by as much as 54%.

MR. SIMON: Tom Simon.

I hope this doesn't sound naive, but are there existing OTC tests now? Or for the influenza, is there a test that could provide an answer to the person taking -- the layperson taking the test that would tell them you've done the test incorrectly, in other words, eliminating the false positive and false negative? Example: red, green, and blue; red means yes, green means no, blue means you did it incorrectly.

DR. LINDSTROM: I can't speak for the entire industry of rapid tests, but there have been recent improvements with molecular tests that can add additional controls in there to see if the specimen was collected properly, to see if there's human genetic material there, for example, to see if the specimen was collected from a human and that there's enough human genetic material there to represent a quality specimen. That's one strategy. But in general, for the rapid tests, it's a positive/negative. The control is more that the test was run properly, more so that the specimen going in is of a respectable or appropriate quality.

DR. PORTIS: Natalie Compagni Portis.

I go back and I wonder what is our goal, if the goal is better patient treatment, and I look at these numbers, about the 42% of patients who are laboratory confirmed and didn't get antiviral treatment and the inappropriate use of antibiotics. And so what would change clinical behavior? I mean, that really seems to be the biggest challenge in what you've presented.

DR. LINDSTROM: Right. So there is a reason for the guidance for influenza, which is basically due to the poor performance of the point-of-care tests where they're non-reliable, and there's a high rate of false negatives. It doesn't rule out flu. So they're saying -- you know, we're saying treat for influenza regardless of the result, because either your rapid test is unreliable, especially the negatives, or your molecular test is going to take too long to get a result in most cases. And so they're saying, well, just test empirically based on symptomatology and prevalence of influenza in a community. If we're looking at -- but that doesn't seem to be working. People are still -- and physicians are still prescribing based on test results, regardless of guidance saying don't believe a negative result. And there's little follow-up of confirmation of the negative rapid test results either. Instead, they're prescribing antibiotics.

And so that's the goal in saying, well, if the goal is to have better tests, and that is the overall goal for the rapid tests and taking that strategy forward to potential over-the-counter tests -- as I mentioned, developing new technologies that meet an already defined level of performance. So there isn't a lot of garbage coming in to weed through. You know, companies and manufacturers understand what the requirements are going to be, and they work towards that and try to mature technologies to meet those needs and that market. I think it's going to take some time to even resolve the point-of-care tests. If we had a good point-of-care test, the guidance -- guidance for treatment would be much different, and there would be more test-based treatments if you could believe that negative result.

DR. PORTIS: What do you think would change, then, clinicians' behavior, though?

DR. LINDSTROM: To have trust in the result. I mean, I think there's too much trust in that negative result right now, and that's apparently --

DR. HENRICKSON: Well, this is a complicated issue. I mean, you're leaving out --

DR. CALIENDO: Kelly, introduce yourself.

DR. HENRICKSON: Huh?

DR. CALIENDO: Introduce yourself.

DR. HENRICKSON: I'm sorry. Kelly Henrickson.

This is a complicated issue, and you're leaving out -- I think one of the big things that drives that percentage is the fact that many of these children or adults who come in, they may be 5 days into their illness with a positive result and only be mildly sick, and all of our data suggests that treating those patients is useless. And so I think that you're taking raw numbers and trying to make the global picture that doctors are into performing somehow. I'm not trying to be defensive there, but I think it's a complicated picture.

DR. LINDSTROM: It is a very complex picture, but even when you look at those that are presenting within the first 2 days with a confirmed influenza test in a high-risk group, it's still being under-prescribed for antiviral medications.

DR. HENRICKSON: But that's because the doctor is again assessing -- or there could be assessments in there where they feel that that patient wouldn't benefit from that treatment. The data is not as clear that -- I mean, yes, we have a study that shows that if you give -- the earlier you give neuraminidase inhibitors, the more chance you have of some clinical benefit. But the benefits are small in the studies that were done, and they were best if you gave it within the first 12 hours basically, okay? So by 48 hours, the data was even -- was softer. It still reached statistical significance. But there's not as good of studies showing that, again, for example, just a child who's 18 months of age and falls within your

high-risk group who has mild influenza, we're treating them as really beneficial, okay? On a global scale, you may reduce complications a small amount, but is it worth treating 100,000 children that way? We really don't have good studies showing the cost-effectiveness and how our antivirals should be used. We use them in the hospital all the time, and we have very little data to suggest that that really helps. Yet, that's the population we're throwing them at all the time. So I think that there's a lot more information and data that's needed to convince clinicians to treat, you know, and so I think that's part of the problem.

DR. RAND: Ken Rand.

One consideration there is the -- if you did have an accurate influenza test, test the ability for the patient might -- the patient's family might not just run out and buy the test. They might buy them ahead of time, depending on the shelf life, have them available and actually be able to call a physician within 12 hours of onset of symptoms and say, hey, you know, my child has influenza. And if the physician knew the patient and trusted them, you could get early treatment. Now, that raises the questions that Kelly raised, you know: Should you be treating 50,000 people to save one life? Or whatever that equation is, and we don't have that data.

DR. LINDSTROM: And that was one argument also raised when we were discussing the presentation today, was if an individual is going to perform testing at home and they're positive, they're going to come in and get the prescription anyways, or they'll phone it in and come get at the CVS or whatever, at the pharmacy. And so would it make just as much sense as a compromise, knowing all of the risks associated with actually putting a test in someone's house? If they were put into a nursing facility or a pharmacy where they could come get their testing in a simplified format, that would be a quicker turnaround. They wouldn't have to go to the hospital or the care facility and get the prescription at the same time. So it's that argument of, you know, if there's testing and then there's treatment and if

you're going to do it at the same time and they're going to come in for their treatment, then why don't they just come in for their testing and have them in an area where they could perform some simplified testing of tests under limited supervision to make sure they're collecting the specimen properly? Or even collecting a specimen, then dropping specimens off at the CVS or Walgreens or whatever, and having them tested there with a test and then receiving a prescription within 10 minutes or 30 minutes or whatever.

DR. CALIENDO: Angie Caliendo.

So this is an important point, and it gets back to what Rick Nolte was saying. We have technologies that could be used in those minute clinics that are higher quality. They require an instrument. You can't have that in a patient's home right now. They're going to come in and get their kleenexes and cough drops and decongestant anyway.

DR. LINDSTROM: Um-hum.

DR. CALIENDO: So it's an interesting middle ground, collect your specimen, bring it in, or even have your specimen collected there.

DR. LINDSTROM: Um-hum.

DR. CALIENDO: I have a question for you regarding the -- I think they were called special controls, those things you listed for rapid antigen testing for flu.

DR. LINDSTROM: Yes.

DR. CALIENDO: Could we apply those to over the counter before it's actually been enacted for rapid antigen testing?

DR. LINDSTROM: I'm not going to speak on behalf of the FDA, but --

(Laughter.)

DR. CALIENDO: So Steve, does it have to -- or Uwe, does it have to be already in place for the rapid antigen tests before you could put that standard in for an over-the-counter test?

DR. GITTERMAN: I don't believe so. I would double-check.

DR. GUTIERREZ: So there's an opportunity to do those de novos, in which case the special controls are put in place as we clear them, if we decide -- if it goes to Class II.

DR. CALIENDO: Okay. So what I'm going to do, at the advice of Shanika, is I'm going to switch this to our open discussion, our Panel deliberations, so that we can have a broader conversation here. So we will officially begin Panel deliberations.

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 all persons who are speaking to please introduce yourselves. It helps the transcriptionist.

We will open the floor now for a discussion. You can bring back any of the speakers for questions if you need to. We're going to discuss and deliberate until about 12:15, and then we'll have additional time this afternoon to do the same.

So Dr. Nolte had a comment, so let's just continue. Oh, go ahead. Sorry.

DR. NOLTE: Rick Nolte.

Just as we move forward with this, I think the rapid immunoassays for influenza set a sort of good example. We don't want to make the same mistakes that were made whenever -- I mean, to have a slew of FDA-cleared diagnostic tests that have sensitivities in the 60s, 50s, 70%, I don't want to see that happen with over-the-counter tests just out of some perceived need for speed or patient access. I just hope we keep that in mind as we move forward.

DR. CALIENDO: Angie Caliendo.

I would say the same thing for chlamydia. We don't need to go back to the days of the EIA.

Dr. Gitterman, we had kind of gotten you talking and then cut you off. So if you would like to finish what you were going to say.

DR. GITTERMAN: Thank you. Steve Gitterman.

I just wanted to actually address two questions very quickly: One, the point you made, Dr. Simon, about invalid results, that's actually the holy grail. The best possible case would be if for whatever reason you make an error as a lay user, in fact, the test would come up as invalid. So that's a terrific way, in fact, to mitigate risks if, in fact, you know that -- you know, if you again could do the flex studies or the human engineering, if your device was able to do that. Unfortunately, we're not at that stage. But just a very quick example of -- adding too many drops of developer make your negative control positive. That would be a great mitigation of showing your test was invalid.

So really, as Dr. Conenello had mentioned, the real goal overwhelmingly will be is, if you could, in fact, address any possible false positive or false negative result, other than biological false positive or false negative results, as invalid results, that would be the ideal scenario. I did want to make a comment -- oh, does that answer your question, sir?

MR. SIMON: Tom Simon.

Yes, it does.

DR. GITTERMAN: Yes. And in fact, if you can tell us how to do it, there's a job here for you.

(Laughter.)

MR. SIMON: I'll work on it.

DR. GITTERMAN: But Dr. Portis, I did want to mention your point. And again, I don't want to revisit the discussion, but when you were talking about antibiotic overuse -- and again, I think Dr. Henrickson addressed this very well -- there's a lot of physician behavior involved, and sometimes physicians do it for reasons of benefit-risk. It may not be appropriate, but in fact, it's their assumption of benefit-risk to use antibiotics. And just a plug. We have a meeting coming up in November regarding some of the newer markers,

which are endogenous markers or expression factors completely independent. And Dr. Lindstrom did -- you know, I thought it was a terrific talk. But by the same token, it's not a diagnosis of pneumonia. It's detecting the presence of pneumonia in the same way group A strep, as mentioned before, you know, has a lot of colonization.

We could all assume a healthy person who then, you know, becomes ill acutely and has a positive influenza assay, in fact, due to influenza, but a few days in or later on, given physicians have read the literature to say a very common cause of bacterial -- secondary bacterial infection is because of primary viral infection, it may become a little mixed. And other assays are needed to do that, assays they can do endogenously to say is it more likely viral or is it more likely bacterial? And as those evolve, it may be a combination of the two, but there is, you know, movement in that end. I don't think we'll be talking about OTC tests necessarily, but we have a meeting coming up in November to talk about one of those proposed markers, which I suspect will be quite interesting.

MR. KIMES: Regarding the topic of validity, you know, those are typically for the test itself. Did I run the test correctly? And I think, you know, especially for some of these that have sampling challenges, the validity needs to also be able to look at did I sample correctly so that I can actually get an accurate result? So I can run the tests perfect every time, but if I don't have the right sample, it really doesn't matter. You know, I think that is the greatest challenge.

DR. CALIENDO: So Angie Caliendo.

But you know, think about it. How are you going to do that? Let's go back to group A strep. How can you tell if I've rubbed the inside of my cheek versus my tonsils? You know, for some of the tests, just finding human DNA would be helpful, but not always. And so I think the challenge is going to be enormous.

Go ahead, Dr. Harrell.

DR. HARRELL: Yes, Lizzie Harrell.

I wanted to also revisit the group A strep because I have taught in the medical school at Duke for almost 25 years. One of the tests we always do, we always have the students do their throat swabs, and I can tell you, even though they know how important it is to get them to do it correctly on themselves, it's so difficult, unless we can get some way to have a mouth open so they can't -- a kid could not move very much, it's going to be difficult to get a swab in the tonsillar area without getting some contamination from somewhere else. So that was my question or comment about the group A strep, if you could have a test where someone with colonization would not be as concentrated as getting the group A strep from the tonsillar area. I'm not even sure if that's possible. It's going to be a problem.

DR. HENRICKSON: I think --

DR. CALIENDO: Introduce yourself.

DR. HENRICKSON: I'm sorry. Kelly Henrickson.

It's not a problem that you hit other parts. It's that's where the group A strep is.

DR. HARRELL: Exactly.

DR. HENRICKSON: Okay. So if you do, you know, a deep-throat tonsillar swab and you hit other areas and it's positive, it's not a problem.

DR. HARRELL: Exactly. I agree, um-hum.

DR. HENRICKSON: Okay.

DR. RAND: Whoops, sorry. It didn't turn on. Ken Rand.

Just a comment on the group A strep, but -- and then I want to make another comment, but that it's possible you might be able to get some white cell markers in there as a marker of inflammation, and that might allow you to distinguish between the cheek swab and the swab from an infected area of the tonsils. From my point of view as a laboratorian, sensitivity and specificity is basically the most critical element in all of this. If we don't have

very, very sensitive and very, very specific tests that the general public is using, we're just going to confound people's problems as opposed to benefit them. So I think those criteria might be definable, maybe not here today but over time and with some of the studies that have been discussed. But I'd really push for very sensitive and very specific testing.

DR. GAYDOS: I think that's a very valid point. Charlotte Gaydos.

It's a very valid point that we -- for over-the-counter tests, we need increased sensitivity and specificity, and I wonder if it's time to abandon assays that only look for proteins and think about whether or not we can have assays that are actually amplifying DNA or somehow amplifying a signal of a protein, because what we don't want to do is have tests on the market for some of the earlier tests like we had for chlamydia that are so bad; they were approved when they were compared to culture, and we now know the gold standard of culture is pretty tarnished.

And so these tests are coming along, that there are many small companies that are working on making amplified tests that will increase the sensitivity and specificity. But in answer of your question about how you tell a cheek from a throat, one possibility of getting around that is to not have people swabbing their own throats but having a partner, a mother, a companion, somebody, a family member, in a pharmacy having the pharmacist take the swab so that you make sure that you have a good specimen, because mostly in the laboratory we say garbage in, garbage out. And so you really need good specimens. And to get specimens that are less than perfect, you can counterbalance that with increased sensitivity. So it's a tradeoff.

DR. BEANAN: Maureen Beanan.

So in speaking with the community about these types of tests over the past few years, some companies are considering the use of videos. So videoing, creating a video of how to take a proper sample, because people will video anything.

(Laughter.)

DR. RAND: I like the idea of the video.

DR. HENRICKSON: I'm sure that's on YouTube already.

DR. RAND: Ken Rand.

Could the video be on the swab itself and part of the test?

UNIDENTIFIED SPEAKER: There you go.

DR. BEAVIS: And this is Kathleen Beavis.

Just sitting on IRBs, one of the big issues that come up is are people literate? Can they read the instructions? You know, I don't read all my instructions with things that I get. What about people who have more challenges? And this is where I think -- you know, we've done a lot of trashing of the Internet today, but this is where I think the Internet could be hugely beneficial, whether it's on a company website, whether it's wherever, if there can be videos, not just about how to collect a specimen but how to, in real time, run it. There can be pictures as to what good results are, what indeterminate results are. And if we want to go totally crazy, we can do what all the kids do and say the question, and they take a picture of it and they can send it. Or they do what I do when I don't know what a parasite is. I take a picture of it and send it. And I agree with you, sensitivity, specificity, prevalence, positive predictive value, that's where, you know, thinking is based on. But I think we have a lot more opportunities today to be able to spread opportunities for testing and, you know, try to take advantage of it.

DR. CALIENDO: Go ahead, Kelly.

DR. HENRICKSON: Kelly Henrickson.

I agree with all the comments that are being said. Right now, I don't believe that we are at a place where we have inexpensive, cheap amplification tests for these analytes that we're talking about right now that can be taken home and cost $10. And so part of BARDA

is at work with -- our goal was to look at all these over-the-counter influenza tests and -- point of care, sorry, not over the counter. Sorry, all of the analyte-specific antibody-antigen tests that are point of care.

And so we evaluated in our laboratory, through BARDA, all of these assays. And to answer one of the questions earlier, it appears to be the chemistry, because of what was talked about, about how they set up the -- how we originally allowed -- we, as the FDA and society -- allowed them to report their data, it allowed for a big variation in their chemistry. So even though they're all antigen-antibody, there's a big difference for each company's test. And we have reported, through this work, that there is not only clinical -- so you heard all the clinical results, right? You guys won't believe -- excuse me, that's my Midwest informality -- how much analytical difference there is between these assays. Okay, there's a huge analytical difference between these assays in their sensitivity.

And the stuff we found supports all of their conclusions, which is that you need special controls and you need to -- we even found that every child's and adult's clinical specimen had different amounts of inhibition for all of these different assays, and it's mostly IgG and antibodies to the nucleoprotein. And so you really need special controls and sort of a synthetic respiratory secretion kind of model to test these assays in, to have a standardized way of evaluating them. The good news is that even though there was huge analytical differences, there were some pretty good players, mostly with the readers, okay, that were, I think, this model that Angie -- which was mentioned about using the pharmacy, so I'm just speaking about influenza now, but using the pharmacy and one of these readers, I think, fits into the current technology we have. So I think that really is the most promising for good sensitivity and specificity and specimen collection.

DR. CALIENDO: Go ahead.

DR. GAYDOS: Charlotte Gaydos.

That might be a good interim step for a pathway, going from laboratory testing to actually testing over-the-counter at home, is the use of a pharmacist. There are huge groups of pharmacies that are investigating performing point-of-care tests. They already give vaccinations. They can send in insurance. And that's another problem is how much these tests will cost and whether or not the patient, buying it themselves, could ever turn in the insurance to get reimbursed for a $40 HIV test or maybe there's an $80 chlamydia, gonorrhea, and *Trichomonas* test.

But a pharmacist can bill, they can bill insurance, and they have a lot of laboratory training, so -- in their training. And there's even a pharmacy certification program that is online where a pharmacist can be trained to perform point-of-care tests and get a little certificate that they've gone through the training program. So that might be one way that we could move along the pathway, especially for some of the samples that we're worried about how well they're collected. We don't have that much problem with STDs because people do a pretty good job of collecting them, but it is a problem with throats and NP-swabs.

DR. CALIENDO: So this is Angie Caliendo.

So just to comment, though, we're here to help them about point of -- at home. So I agree totally, but we don't want to drift over there too far. We need to stay focused on if you're doing this at home. I think, Barbara, you had a comment. And then we've got Peter. And Maggie, do you have one, too? No, wait. You're third.

(Laughter.)

DR. VAN DER POL: So actually, this comment is coming from a few comments back. But as we're talking about, you know, that sensitivity and specificity are sort of the holy grail as per usual, I think that one of the things that we do need to keep in mind is that even once approved, if we go down this route and we say OTC tests are a good thing, in the same

way that point-of-care tests were a good thing, there needs to be a mechanism -- and I think this really needs to be considered up front -- for monitoring the performance so that it's hitting the performance the way it said it did when it was originally produced, and also for, you know, removing those products from market that performed well, compared to what we knew, when we knew what we knew, but no longer perform well based on what we know now.

And I don't feel like those mechanisms are really in place. But once you start letting -- it's one thing when you have a result and a clinician takes that result into account with the context of the person because they're interacting with that person. But now, if you start to remove that clinician from the picture and that interactive process, now the sensitivity and specificity become even more important, I think, right, because these people are going to make decisions, whether that decision is to go into healthcare or whether that decision is to try to get treatment. So I think that there needs to be consideration in advance of some sort of monitoring process to make sure these things should stay on the market.

MR. WOLFF: Thank you. Just two points.

So the FDA Executive Summary that was provided, I think, is really an excellent document. You can see a lot of work went into that. And one of the things that they point out there is the OraQuick test. So I just Googled OraQuick, and there are countless numbers of videos on how to use it. You know, the company maintains a website. There are a lot of tools that can be used to mitigate risks and to help ensure that people use the test and interpret the test properly at home. So it should be kind of a reference, I think.

DR. HAMMERSCHLAG: Well, I was going to talk more about the problems of collection, but I just want to agree totally with what Barbie said. And as for the issue again with the OraQuick, it would've been an example of how this thing would work, but it looks

like the uptake has not been very big. Has it? The uptake has actually been pretty minimal and the follow-up -- it has different -- HIV has a different set of implications. But just to go back again to throat cultures, I don't want to perseverate, but as a pediatrician, it is not an easy test to do. Even pediatricians don't get it, especially if you have an uncooperative subject, and most of these tests will be done with this group A strep in children, and you get -- there's a very, very -- especially the kid -- a gag reflex, and you often cannot visualize the tonsils.

Now, very possibly, if you had a NAAT, just like we found out that it's sensitive enough in urine, whereas obviously for chlamydia or gonorrhea, the culture is not going to be, it's very possible you can get away with a less rigorous test. But as it stands now, and I said this earlier, you're supposed to come out and actually do both tonsils and come out with a piece of the tonsil on the swab. And there are studies that have been done showing that repeated swabbing, you actually start increasing the sensitivity very dramatically. So I think that is going to be -- for a layperson, it's going to be a major problem because it is -- for a child who's not going to frequently submit to this easily.

DR. PORTIS: Natalie Compagni Portis.

Just going on the heels of so many comments, I'm all for empowering the patient to take a more active and involved role in their healthcare, and I think back to the issue of access. When we start talking about videos or online information, that's not accessible to everyone. It's not accessible to a lot of people. And so even some of us who have access to these things, we get those reams of paper, and I think you said, Dr. Beavis, we don't read them; we just toss them out. And so I'm concerned that if the goal is to have patients have more access, that we don't really get that, even if we have a very specific and very sensitive test, that for a lot of people, they just -- they aren't going to have the information to do it accurately. And the comment about communication between the doctor and patient, I

think it's really important to do these things accurately. We already see, once you have an accurate test, that often people aren't being treated to the best of the doctor's ability. So I think taking out those safeguards maybe isn't the best for the patient.

DR. MARTENS: Mark Martens from New Jersey.

I'd like to ask the FDA to answer Dr. Van Der Pol's question because I am also concerned. I know the FDA -- and the reason we're here is to approve tests. I'm under the impression the FDA doesn't address when to take a test off the market, that it's CMS that does that. And the second question is or the second point is, as Dr. Gaydos mentioned, you can take a vaginal swab and the patient can do it very well, but it's with amplified testing, and if you don't use amplified testing, you don't get it. The women -- you know, the vagina is not an easy organ. It's probably the most complicated organ in the universe, but it's -- you don't -- women don't put a swab in and hit the end of the cervix. You know, it's only because the amplified tests are so sensitive.

So unless you do an amplified test, you're not going to get good results, and you'll have to get the end of the cervix, which no one does, because we've done the studies looking to see if patients can put imiquimod on the cervix for dysplasia, and they miss it all the time. But does the FDA know -- can you tell us how a test is removed from the market?

DR. GITTERMAN: I can give you two answers -- and a note to myself: Have legal counsel, regulatory counsel every time we have one of these meetings. But the first question is we do have a well worked out mechanism for recalls and corrections. So if a test comes to our attention, or more commonly the manufacturer's attention, that is mis-performing, we have a very well worked out mechanism, and there's also, of course, a mechanism for reporting, you know, adverse events to the FDA that's very commonly used.

And now, just to answer this clearly, that in the setting of a moderately complex test in a laboratory, because we can't underestimate the sophistication of laboratorians and

there's a lot of mechanisms for them to notice something is mis-performing with a test -- one is, as you mentioned before, Dr. Simon, even if a test just has more invalids than expected, that's a clue that something is going on. But again, a lot of tests have reflex testing, etc., that give us a clue.

Regarding the question of taking something off the market, that's far more complicated. The regulatory structure that we have now where better tests come out, so to speak, is called progress, and there's no mechanism to take off tests that may be very, very old as long as they're performing to the original specifications.

Now, again, not to make this overly complex, as Dr. Caliendo and I know Dr. Lindstrom had mentioned, if there are special controls that, in fact, have mandated annual testing -- now in his case, though, again to be very specific, there's a very good rationale why you would expect that because the circulating virus may change, characteristics of the virus may change. We also see this actually just in bacterial and AST tests. Bacteria evolve, different mechanisms come up. But if it's in the special controls, that's a mechanism. But again, if better tests come along, the assumption will be the market will take care of it, but again, there's a lot of balancing, a better test versus a much cheaper test or something that's -- you know, that's point of care, so to speak. There's a lot factors in it.

DR. CALIENDO: So Angie Caliendo.

So what I'm hearing you say is very important for this Committee, which is we can't predict the future, but we have to make clear recommendations on special controls today, because I think what Barbara said is incredibly important. And if you don't have a mechanism to get them off the market, then it is on us to figure out the highest standard that we can -- a number, what we can do with special controls to ensure a standard of performance, because there isn't going to be a way to reverse to these once they're out

there. And you know, we've lived through this with chlamydia EIA. I hate to keep coming back to it, but it stayed on the market long before -- long after it was useful because it was inexpensive and labs, public health labs had automated it. So this is important for us to hear.

Go ahead, Uwe.

DR. SCHERF: Yeah, Uwe Scherf, FDA.

I would like to add one additional point, I think, because what you just said is very important to us, too. Remember, for the rapid tests, as a scenario, when they were actually cleared for use, I mean, there is the requirement for follow-up testing, yeah, but I think -- and that's what this audience also needs to kind of take into consideration. This is normally not done, that really the follow-up and some of these results for children and so on is really not executed on, and that has, of course, kind of challenged us in a way to move forward with some of the ideas on the over-the-counter. But I think it's very important what you just said. If you are coming up now with recommendations, please also consider what is then recommended. Is that something that is really doable in the overall and everyday setting of the hospitals as well as, in this case, doable in the actual home setting?

DR. GAYDOS: Yeah, I totally agree with what Angie said is that because some of the older tests are cheaper, whether this is for influenza or for chlamydia and gonorrhea, people will still use them because they're cheap, even though they are not up to the quality of the better tests that have evolved and are evolving. The CDC recommends that point-of-care tests for STIs not be used. Their recommendation is that vaginal swabs are okay and recommended to be used if NAAT testing is performed. So I think we have to realize that as we move forward away from EIAs and we move forward away from some of the rapid tests for influenza, we probably are going to be moving in the direction of some sort of amplified test to increase the sensitivity and the specificity. We certainly have seen that over time.

And these tests are evolving. There are many companies that are working on doing amplification of some sort, either amplifying the signal or actually amplifying the actual organism, DNA, RNA, or whatever. So we do need a method to take tests that don't perform well, that are cheap and convenient, off.

With regard to over the counter, it will be possible, I think, in the future to have amplified tests that will not need special equipment. Everything will happen right in the cartridge, the extraction, the amplification, and the reader, and then the patient can throw it away. So what we need to know is, I think, how to perform the studies to see if these work. It's incredibly difficult to know how the studies could be done to even get over-the-counter use.

DR. GITTERMAN: I just want to raise a couple points. One is that the devices and, of course, tests are required to have quality systems. So there's a lot built in on the front end. Influenza -- and to again get -- I don't want to get into the devil is in the details. That's going to be this afternoon. But again, if a test is performing up to its original criteria, if originally it was cleared by FDA, whether it's over the counter or whatever, and there was 60% sensitivity, as long as they keep performing at 60% sensitivity, we can't take it off the market. I mean, there's no legal way. That's beyond special controls. So that's an important point, and it gets back to the point in which you hit the nail on the head at the beginning: What's the standard that you want to set? Because, again, we're looking to some guidance, and it may not be possible regarding what that baseline might be.

The second point I would just like to make, if I can remember it because I'm an anxious speaker, is -- if you give me one second, it will occur to me. Oh, the devil in the details. Now, it's easy for influenza. Influenza, we can, you know, call up Dr. Henrickson and say we're sending you a bunch of, you know, samples. We think they're going to be the circulating strains. How did the tests perform against that? That's a fairly good in vitro test.

Unless gonorrhea -- or when I say -- is fundamentally changed, some type of antigenic change or some type of chromosomal, depending on what it is that you're actually doing molecularly or antigen-wise, it's fundamentally changed, in that case, to say is it performing as well year to year, one is either you have, you know, a structured sample which one would hope is already part of the QSR, or two, then you have to go out and get -- you know, find that random sample or something that targets you to suspect it. In real life, that's very difficult to do, and the fact is, we have a regulatory mandate to be as least burdensome as possible.

So there are a lot of -- it sounds great to say, oh, we're going to have a special control to make sure it works, but it's not that simple, and it certainly will come up this afternoon. But you know, sometimes committees come up with things, and you say, oh my God, we can't possibly do that. But it's very interesting. But the fundamental question of what -- it's amazing, because I think of a microcosm -- just the last 10 minutes have been incredibly interesting -- a microcosm of safety, as Dr. Hammerschlag said, and what the performance should be, you know, I'd really emphasize.

And one very last thing, which I'll skip -- I'm talking too much. Well, the OTC regulations are regulated under the regulation for that device. And as Dr. Caliendo has been steeped in, there are Class I, Class II, and Class III devices. The OraQuick HIV is a Class III device. It's under the strictest regulation. Anything they do to change the test in any way, shape, or form that's even remotely significant gets reviewed by FDA. There are a lot of controls. It's a little less under Class II. One might argue, substantially less, depending on what they have to contact us with. And then there's Class I. So again I think, as Dr. Conenello pointed out in her talk, that might have gone past people; these are all Class II devices, or it may be in the background. So there is some regulatory control over the device. They can't fundamentally change it without letting us know and without validating

the performance. I'm done. Sorry.

DR. VAN DER POL: So I think that the piece that I tried to raise, but I'm not sure --

DR. CALIENDO: I'm sorry, introduce yourself.

DR. VAN DER POL: Oh. Barbara Van Der Pol.

Is that the tests substantially perform, they performed well, but they performed well because it was against a poor standard. And we all know that, and we can actually do the mathematical calculations, and we can say this test, in its package insert, says it's performing at 90%, but that was against something that was only 60% sensitive. And so if you do the calculations, it's only performing at 54%. But we didn't know that when it was approved, so it was approved as a high-quality test at 90%. And I guess my point here is, is to say that we need a mechanism in place that's not necessarily directed specifically at any individual vendor, but that is to say, okay, this is what the current standard is now. But as that standard evolves, we have to reevaluate anything that was approved under older standards, and how to do that reevaluation is unclear to me.

DR. GITTERMAN: Again, we need discussion, but that may not be possible under the present regulations because we can't write anything that's not regulatorily --

DR. CALIENDO: So Angie Caliendo.

So I think what we have to do, Barbara, is do the best that we can with what we know right now. We have to set the most appropriate standard with what we know. And I think what we've all said is molecular testing should be the standard by which these tests are compared, not culture, not an antigen test. And I think that's the best that we're going to do.

Maggie, you're next, and then Lizzie.

DR. HAMMERSCHLAG: Just to reiterate that, with using NAATs for both chlamydia and gonorrhea, we have two examples where the target changed. There's *Neisseria*

gonorrhea for those -- well, you know, it will continually exchange genetic material with other *Neisseria* species throughout its life cycle. So some of the DNA-based NAATs we're actually losing and becoming less specific. And in some cases, one of the earlier iterations, which was the Amplicor, was having some major problems. Then there was the mutation that occurred in the plasmid, the Swedish variant of *Chlamydia trachomatis*, where it actually had a deletion right at the sequence where this particular test had its target, so -- and there was no other way to pick that up unless you were doing another test.

So these things -- that, I think, was obviously not a direct cause of the test, but what happened obviously is that they found out suddenly they weren't picking up any more chlamydia, but -- and it was just one of these mutations that happened at the wrong time and the wrong place. So these things are -- it's like a moving -- literally, a moving target, and the biggest problem is once the cat's out of the bag, the train has left the station, how on earth are you going to do the analytic -- any kind of analysis to determine if there's a problem, especially if you're not even collecting any data on what are your prevalence is in your population? I mean, in Sweden, they saw something funny was happening because they were doing surveillance. So nothing is ever 100%.

DR. CALIENDO: Go ahead, Lizzie.

DR. HARRELL: Lizzie Harrell.

I agree with what has been said already, but I keep coming back to the fact of how we can get a perfect test or get a test that is as sensitive and specific as we possibly can for over-the-counter use. And then the next part is how do we then get all of this myriad of different users to come to some -- give them some instructions that will allow them to use it in a way that will yield the same results that we are getting when we are doing it as scientists with all of our knowledge? So the big thing, I think, is getting the perfect test as well as we can for over-the-counter use and then working just as hard on the instructions

for the users because that is -- that's where the devil is going is to be in the details, how to get them to understand how to use it.

DR. RAND: Ken Rand.

Could I make a couple of comments? One is -- and I'll take my chances on this one. But the FDA has a role in, for example, drug safety, and if a drug performs totally satisfactorily in terms of curing patients but has a 1 in 5,000 fatality rate, you pull it from the market. So if there are adverse consequences from a drug that you regulate, you can pull it. Why would that not be true for a diagnostic test when 60% sensitivity results in adverse consequences?

DR. GITTERMAN: I think that's -- well, the first thing would be -- and again, these are not -- as more information is learned, again, if the test is associated with adverse events that we weren't aware of, certainly, that's a consideration. The idea, though -- and again, if you have a test that you get cleared at the state of the art now that's 60% and you perform up to spec, we don't right now -- outside of regulatory rulemaking, which is a difficult process, we don't have a mechanism to say all right, now there's tests for 85%. One would hope that the medical community would advise against it and that people wouldn't do it, and there would be different ways.

But if you're looking at FDA to say we've made a decision that the new standard is 85%, and therefore, given that every test has benefit-risks and there's always a risk of a false negative, that there's two things here: One is learning that the risks of a false negative are more significant; that's one issue. But the idea that, absent that, that the original spec now, you know, has changed or the state of the art has changed or the community standard has changed, we don't really have a mechanism to do that, outside of regulatory rulemaking.

DR. RAND: I just think, in principle, it's not different from your regulation of drugs.

So, for example, if somebody does a rapid strep test and gets rheumatic fever from a negative, that's sort of the kind of adverse outcome that you get from a drug.

DR. CALIENDO: Okay. So I understand what you're saying, but we're not going to change the FDA approach to this right now, today. So we get it and we don't like it, but it's reality, so we need to move on in reality. Yes.

DR. MARTENS: I agree, but the only thing I can ask is if the FDA would then set a very high bar for approval of the first test -- I don't think there are going to be predicate devices for these tests. So I think that benefits outweigh the risks.

DR. CALIENDO: Well, that's part of our -- Angie Caliendo. That's part of our discussion this afternoon: What is that bar?

DR. MARTENS: Yeah, I think you said --

DR. CALIENDO: We're going to have to define those performance characteristics. As someone mentioned earlier, we're going to have to define for them or at least help the FDA -- how would you do these studies? This is the detail we need to get into.

DR. MARTENS: Yeah. This is Mark Martens.

I think we should set the bar very high. I don't want to see what happens with a herpes serology where the CDC has got to waste space -- not waste space, but use space in their 120-plus page recommendation telling us doctors what tests we should use for herpes serology because there are other tests on the market. I don't think that patients and the public can do it. I think we've got to try to protect them because if there's a $2 test or a $5 test on the market, they'll take that over the $30 test no matter what we say.

DR. HENRICKSON: So Kelly Henrickson.

So speaking just for influenza, can we -- I think it should be analyte specific, as you said, and can we as a committee actually say that no matter what special controls we describe, no matter how sensitive and specific a test, if we have enough concerns, can we

say we think, for this analyte, there shouldn't be over-the-counter tests? Would that --

DR. SCHERF: Actually, that's our objective for this meeting because I mean, as you saw --

DR. HENRICKSON: Because I have to say I'm worried about true positives. There's 2 to 4 million children who may become infected every year with influenza, who you may -- it may not be in the public health's good to have the moms buy these tests and test them. So I'm concerned about even if we do all of this and we have a great test, that true positives might be a problem.

DR. SCHERF: No. Understand, what you saw even from the structure of the talks, right, they are very different analytes that we presented and we selected and very different challenges, yeah. And I mean, we somehow kind of selected that very kind of carefully to maybe allow the discussion that is starting now; that is, it is not possibly likely that you can make recommendations for general approaches there. It might be much more fruitful to have actually very, very specific ones for some of the analytes. Consequently, of course, we only will be able today to maybe address some of the analytes and not all of them because we only had three today.

DR. GITTERMAN: I would just say we're asked not to go through the questions in detail, but we've obsessed quite a bit of time having very specific questions to ask to the Committee. So the first thing in the -- or perhaps the -- maybe not the first thing. But early in the afternoon, Dr. Feldblyum will be presenting the specific questions because we do have things we want to get answers to, or at least have a discussion about, and one of them is perhaps these aren't ready for OTCs at this time. I would mention, too, there was a previous Panel meeting -- how many years ago was that, Angie? Before your time.

UNIDENTIFIED SPEAKER: '89.

DR. GITTERMAN: '89, on group A strep, addressing the exact same question. And in

fact, the tests are a lot better now. Well, it depends. Maybe not. So, you know, again, we're revisiting it.

DR. NOLTE: Yeah, the whole concept about whether to have over-the-counter tests, I think, is what we're -- I'm still struggling with because what I see now happening in the diagnostic space is the move towards more -- to better point-of-care tests that are -- where results are delivered in some sort of healthcare setting, whether it's a pharmacy or a clinic or an emergency room. And now we're jumping -- we're leaving that behind, and we're jumping to over-the-counter tests, and frankly, I've not seen any compelling evidence that suggests that it would do the public any good. I mean, I hear a lot of limitations. I'm having a hard time seeing the need and that's -- I mean, that's probably going to be a big part of when a manufacturer comes to the FDA, whereas -- I mean, the analytical part we can talk about all day long and we'll have hours of discussions about that. But how do you get to, you know, the need, the clinical value, the underserved populations? Are they going to have access to this? The linkage to care piece, which is a part of every one of these things, is absent. Yes.

DR. GITTERMAN: But that's why we invited you folks.

DR. NOLTE: Yeah, that's what I mean.

(Laughter.)

DR. GITTERMAN: But we could decide that we actually want some input.

I might suggest, Shanika, that maybe this is a good time because a lot of discussion seems to be about the issues for the afternoon. Maybe Dr. Caliendo would want to consider lunch.

(Laughter.)

DR. CALIENDO: We're almost there, Steve. Hold on, there's one comment over here.

MR. SIMON: Tom Simon.

In listening to all the discussions and being a consumer and having done various tests myself, the simpler is better obviously, and what we have now is what we have now. What it is, it is. But as I see it going forward, the tests that would be good home tests would either be saliva or blood. It would be simple, if they could do it, because most of the people -- not all. I don't care how simple it is, most people would be able to perform it. If there's a relationship, say, with influenza and blood, if there's a relationship with gonorrhea and saliva, strep throat and so on, if there's a relationship, the easiest thing to do is prick your finger, put it on there, positive or negative. There can't be either -- very little chance of having a false negative and a false positive.

However, I will say one thing. I just had a colonoscopy, and I followed the directions religiously. I got there, and they said you can come in early. I said oh, okay. Why? Well, someone did not follow directions. I said what was that? They drank 2 hours before. And if they told me once, they told me 50 times, don't drink anything for 4 hours. And I said how could they have made that mistake? And they threw up their hands. So no matter how simple it is, it's going to be misused, mistakes are going to be made. But to me, the most simple and the most obvious way to go, whether it's today or years from now, is either a blood test or a saliva test, if you can test for influenza or for strep or for what other disease.

DR. CALIENDO: Go ahead.

DR. PETTI: And just to add a different perspective, a lot of us have been affiliated with academic medical centers and extremely sophisticated laboratories. But having directed labs that are -- many are outreach clinics and laboratories in rural areas, we assume the infallibility of specimen collection at the bedside, but is every medical assistant, PA, and nurse practitioner well versed in the practice of specimen collections, and really understanding the importance and the value of having a pristine specimen collected and its impact on test results? So when we enter this afternoon's discussion, I think we all should

be mindful that infallibility certainly does not exist in our healthcare system today.

DR. CALIENDO: Okay. Thanks, Cathy.

So, at Dr. Gitterman's request, we're going to lunch.

(Laughter.)

DR. CALIENDO: So we're going to break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We'll reconvene at 1:15 in this room. Please take your personal belongings at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

Thank you.

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

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

(1:15 p.m.)

DR. CALIENDO: Okay, so it is now 1:15, and we'd like to resume the Panel meeting. We're going to 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. Craig will read the Open Public Hearing disclosure process statement.

MS. CRAIG: 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 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, the financial information may include a company or a group's payment of your travel, lodging, or other expenses. 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 the meeting.

FDA has four requests to speak -- five --

(Laughter.)

MS. CRAIG: -- requests to speak prior to the final date published in the *Federal Register* notice. Each speaker will be given 5 minutes to speak.

DR. CALIENDO: So I just want to remind people to please speak clearly into the microphone. The transcriptionist is having a little difficulty understanding some of us on

the Panel. And again, to give your name before you speak. So we'll now begin the Open Public Hearing.

The first speaker is Michele Schoonmaker. Please come forward to the microphone. We will ask that you speak clearly to allow the transcriptionist to provide an accurate transcript of the proceeding to this meeting. At the conclusion of all the public hearing presentations, there will be time for questions from the Panel members. And as was stated earlier, each speaker has 5 minutes.

DR. SCHOONMAKER: Thank you. Good afternoon. My name is Michele Schoonmaker. I'm the Vice President of Government Affairs for Cepheid. Cepheid manufactures molecular diagnostics and clinical laboratory tests primarily for the detection of infectious disease and for cancer. We thank the Agency for holding this public meeting and for the opportunity to comment on the appropriateness of clearing or approving over-the-counter diagnostic tests for the detection of pathogens that cause sexually transmitted infections (STIs) or respiratory tract infections (RTIs).

Since 2011 we have commercialized several diagnostic products for STIs and RTIs for near-patient use in non-waived laboratory settings. In 2005, our first flu RSV assay was granted a CLIA waiver, and moving forward, we plan to seek CLIA waiver for nearly all of our tests for those intended uses and eventually would like to move into the home testing marketing.

The potential value of over-the-counter testing is clear: It could increase patient access to targeted diagnostics that with the right treatment could help reduce disease transmission. We acknowledge that additional discussion is warranted to ensure that the benefits outweigh the risks. Specifically for STI testing, there's often a reluctance of infected patients to seek out testing until symptoms become severe, which can result in missed opportunities for treatment and in additional complications for those patients. OTC

testing would likely facilitate anonymous testing, and presumably, patients who test positive, or for those who test negative but still whose symptoms continue, would then be more likely to seek medical treatment, knowing that they are either infected with an STI or have another condition that may require a different therapy. Physicians, likewise, may be more likely to write a prescription for partners of patients that are known positives. At a time when STIs are once again on the rise in the U.S., this could be of significant public health value.

We also support over-the-counter testing for RTIs, knowledge that RTI status could help inform patients as to their own care, including whether they should seek follow-up care from a healthcare provider or if self-isolation is necessary to support workplace- and school-based infection control. Feedback is needed as to whether clinicians would be willing to treat a patient with antiviral agents based on the results of an OTC test, especially if the test was performed after 48 hours of symptom onset. Cepheid recognizes the risks involved in OTC testing, including the impact of false negative and false positive results.

However, the accuracy of products cleared or approved by FDA for OTC testing using existing performance standards may well equal or exceed the accuracy of some products currently in use by many laboratories, particularly for the RTIs. No diagnostic test is perfect. Even high complexity tests performed in the hands of well-trained, qualified laboratorians carry a risk of false positive or false negative results. Certain design features can be built into these assays, such as sample adequacy controls, which were mentioned earlier.

To avoid reporting false negative results with unsupervised self-collection of specimens, most studies to date indicate that self-collected genital urinary tract and respiratory tract specimens work well, as long as the analytical sensitivity of the test is high, so that arguably the performance of the test used at home should not be significantly

compromised in the performance relative to current benchmarks.

OTC tests should meet the standards of "simple and accurate." However, in assessing accuracy, we urge the Agency not to create clinical data requirements that go above what is currently established for laboratory-based test products. Excessive clinical data requirements could effectively restrict innovation and test design and actually reduce the number of OTC products to market. For the evaluation of simplicity, we agree that stringent human factors testing is critical to the success of OTC testing. Consumers need to effectively perform and interpret the test results.

Educational outreach to patients and pharmacists could help mitigate some of the risks associated with test interpretation. Patient loss to medical follow-up and the impact on surveillance of reportable infections will need to be addressed, but these concerns could be mitigated by electronic solutions that facilitate follow-up and reporting, either through patient self-reporting or by the healthcare provider that sees the patient that tests positive or that ultimately writes the prescription.

In summary, we believe that OTC testing has the potential for significant public health benefits in the reduction of infection transmission by increasing patient access to broader detection and treatment of STIs and RTIs. We look forward to continued discussion, and Cepheid will likely submit more detailed written comments to the docket following the conclusion of this meeting.

Thank you.

DR. CALIENDO: Thank you, Michele.

DR. SCHOONMAKER: You're welcome.

DR. CALIENDO: Okay, our next speaker is Charles Sailey from Molecular Testing Labs.

DR. SAILEY: All right, I'll get situated here. Hello. Thank you for having me. My name is Charles Sailey. I am a molecular genetic pathologist and the Director of Molecular

Testing Labs in Vancouver, Washington. We do a large amount of infectious disease and genetic testing.

Next slide, please. Or am I able -- is that what this is for? All right.

So right off the bat, we wanted to put out there that we do, as a lab, support the availability of over-the-counter and direct-to-consumer testing for STD testing. And I'll use STI and STD interchangeably here. Also, I will be using "over the counter" and "direct to consumer" interchangeably, only for the sake of this presentation because of the commonalities between the two, and that's the fact that the test is available directly to a consumer without the intervention of the physician. So those are the things that I'll focus on during my talk.

So we've seen this already from the CDC. You can see, in the bottom right, chlamydia is going up, syphilis is going up, gonorrhea may be. But if you look at the age brackets, there's very specific age brackets that are affected, and these are the teens and early twenties, right? And that's all across the board with these STDs, right? So keeping that in mind, these are the ones we should be targeting. We need to find a way to get this education to these people, to get these people to get testing.

And these people are -- do I point this somewhere? All right.

And these people are the Generation Z, right? So 1995 up to now is the Generation Z group of people, and they have a very different mindset. They're the true digital natives, the first round of people being born into a digital world, right, where it's digital and on demand and you need things quick and very unconventional. We need to find a way to provide access to STD testing in a way that makes sense to them, right? They're the current ones who need it, and they're also the highest risk. So we need to think differently, and we need to think progressively, out of the box, as they say. And we have an ethical obligation to do that as medical professionals. We can't stick to our old guns and say you need to

come in to the clinic, you need to come in to the clinic. There has got to be better ways to do it. You know, we did it in the 1980s and 1990s with HIV. We changed our mindset. We opened up anonymous clinics that people can walk into and get tested.

And now, with this current generation, they have smartphones, they have instant access to the Internet, they have this 24/7 access to technology, and they have a click-a-button, get-it-now mentality. And if they're under the age of 24, they don't want to go and use their mom and their dad's insurance to get testing. They want to find it on their phone. There's got to be an app for that, right? Find that app and order that test, right? And that's what they're thinking. You are not going to sway them from that. If we can offer safe, reliable testing, with their mindset it's going to be a revolution. And you know, we need to respect what they want and their autonomy. It's a new era, as they say, right?

So from the literature, you can see people prefer self-collect over physicians. Nobody wants to go to a physician to get tested. Here is one where 18% of adolescent girls were tested. Fifty-one percent -- or 18% were tested positive, and 51% would not have pursued testing through a physician; 97% said yeah, I would get tested again, only if it was not through a physician, if it was a self-collect method.

Here's another one where 68 of them never had an STD examination, and this is this age group of 16 to 35, and 11% of those tested positive for an STD, and these are people who probably would not have gotten tested. And the vaginal swab and urine collections were almost uniformly preferred over gynecological examination. We see this time and time again; this is a very small subset of what's out there. Ninety-eight percent of college-aged women said it was easier or very easy, and they all preferred it over traditional methods. And then you have vaginal swabs are just as good, it's just as appropriate as endocervical swabs. So we know what the mindset is now. Looking at this, we know what people want. The way we need to approach it now is what kind of tests can we offer them

and how can we do it in a safe way, because they're not going to do it any other way. We're going to lose these people. They're not going to get the testing.

The advantages, really quickly. And we talked about every one of these: privacy; ease of use; minimally invasive; minimal barriers preventing people; more accessible to the wider range; multiple STD tests using one self-collection device; accuracy is there for these tests, and if we have time, I'll show you an internal study that we did where our accuracy was 99%; acceptability.

The last one is what I really want to talk about because this is the one that always comes up; this is the one everyone thinks is their ace in the sleeve: They're going to get lost to follow-up. But you know what? Lost to follow-up versus not tested, I would take lost to follow-up every time. At least they're tested, and maybe 10% of them will get testing, maybe they won't. And I'm being told that I don't have time to go into an internal study, but it will be published, so you'll see it in the future.

Thank you.

DR. CALIENDO: Thank you.

DR. SAILEY: Any questions? I guess not now.

DR. CALIENDO: Okay, our next speaker is Bala Raja from Luminostics.

DR. RAJA: Hello, everyone. My name is Bala, and I'm with a Bay Area-based diagnostics startup called Luminostics. At Luminostics, we're developing a smartphone adapter that can perform supersensitive immunoassays, and one of the first indications we're considering is an over-the-counter screening test for chlamydia. Over the next few minutes, I intend on making a specific argument about why I think the benefits of an OTC chlamydia test outweigh the risks, and this argument has to do specifically with accessibility and an increased screening coverage. And you know, when I say think of the kids and the title, I really mean the 15- to 24-year-old demographic. And you know, like Dr. Bolan

mentioned this morning, this 15- to 24-year-old demographic, it accounts for a disproportionate amount of STIs. They're only about one-fourth of the sexually active population in this country, but they account for almost two-thirds of all new infections. We already know that this is because young people are more likely to engage in high-risk behavior and also because they're biologically more susceptible.

But the question that needs to be answered, especially from a test manufacturer's perspective, is whether this demographic actually desires an OTC test. If they do, will enough of them use it? And if the answer to the first question is yes, the second question is really up to, like, the advertising and marketing abilities of the company that's making a test, right? So, you know, the FDA's Executive Summary for today's meeting cites some publications that answer these two questions and explores them, but I thought I'd present some of my own data.

We conducted a survey of a random sample of 300 sexually active men and women in the 18- to 24-year old demographic in the U.S., and their responses were completely anonymous, except for the age and gender, so we hope they had no reason to lie, and I'd like to highlight some of their responses.

So the first question was pretty basic. It asked them how often they got tested for STIs. So almost 50% of our survey takers had never, ever gotten tested for an STI. That's pretty bad, right? And this answer reflects the stats cited by the CDC in terms of the current extent of the screening coverage and all those things.

So the reasons cited in our survey for why they'd never gotten tested -- and I'm going to focus on the population on the sample that answered "never." You know, these reasons were the usual suspects. They were embarrassment, inconvenience of going to doctor, the cost/no health insurance, the result's going to show up on my parents' insurance bill, that type of thing. And these were a combination of, like, answers they

entered and multiple choices they were able to select. And on another question in the survey, 44% of the sample, the people that chose "never" said they were very likely to want to buy a do-it-yourself at-home test, and this means they selected either 5 or 6 on a scale of 1 to 6, from least likely to most likely.

So I know this survey is not super-rigorous, and it's not a giant sample size -- it's only 300 people -- but the trend is pretty clear, right? So if we were to scale this up, this means that millions of 15- to 24-year olds that would've never gotten tested otherwise would get screened if an OTC test was available. And you know, like with any reasonable level of performance of a test, this cannot be construed as anything but a net positive to public health.

And let me close by citing a modeling study about the effect of increased screening coverage on disease prevalence, and I thought I'd highlight this because this was one of the good ones that wasn't cited in the Executive Summary, which was very well put together. And this was published by the University of Melbourne in 2013. And for a high-risk/high-prevalence population, their model predicted that increasing screening coverage from 44% to 80% per year would reduce the prevalence of chlamydia in this population from 12% to less than 2% in just 3 years, right? I urge you guys to read this paper in greater detail. But in the U.S., you know, to replicate anything close to this model, to increase screening coverage to 80% would be, in my opinion, impossible without the availability of over-the-counter tests.

So I'm out of time, so thanks a lot. I'm happy to answer questions now or later.

DR. CALIENDO: Thank you.

DR. RAJA: Thanks.

DR. CALIENDO: Our next speaker is Myriam Battistutta from Ellume.

DR. PARSONS: Actually, Sean Parsons from Ellume. I'm Founder and Managing

Director of Ellume, which is an Australian diagnostics business. I'll keep this short. Thank you very much for extending an invitation.

This is a 40-year-old fellow with -- on ECMO for swine flu who I looked after in 2011 in a tertiary referral center in Brisbane. There was a realization at this point that, despite the enormous investment and toil over the last several decades, we're yet to really win the war against influenza. It is still a very burdensome disease with more people dying from flu than from car accidents.

I founded Ellume in the belief that enabling -- by creating rapid, robust diagnostics and by linking the results of those diagnostics to appropriate clinical therapy, we would enable people to get diagnosed earlier, to access early appropriate therapy, to reduce their complications, and in due course, to reduce the burden of flu on the community.

Today I'm not here to talk about our products in lots of detail. Suffice it to say that they are a single-use fluorescent detection technology. I would like to look at the status quo and the impact that the status quo has on understanding the benefits and risks of influenza, but with the recognition that these same issues really extend beyond flu to chlamydia and group A *Streptococcus*.

About 2.4 influenza-like illnesses per person per year in America, so that's more than 700 million flu-like illnesses (ILIs). See, not all of those are severe, and not all of those are influenza. But that's a big number. Of those, about -- that's that big line in blue. Of those, about 30 million people actually get flu each year. There are approximately 35 million influenza-like illness presentations to clinicians, as per the National Ambulatory Medical Survey 2012, and of those, approximately 4 million of those are actually influenza. And there's about 100,000 notifications to the CDC each year. The point I'm trying to make here is that about 8 in 10 people -- 8 of the 10 people in America that get flu do not see a doctor. They struggle on in the community. They transmit influenza at their workplace. Their

children go to kindergarten or school and transmit flu. And in order to address those people like Steven who end up with severe complications, we need to do something about the iceberg in the community of people with influenza.

Whilst 4 million people with flu that go and see a doctor are critically important, they're the people who are likely to be at high risk and likely to suffer complications. Without dealing with that burden of disease in the community, we would be missing the opportunity to make a dent in the number of people and the burden of disease.

The status quo, from a diagnostic perspective, is actually very poor. So the self-diagnosis of influenza -- the blue bars are sensitivity, the red bars are specificity, and the green bars are the combined accuracy issue and 10% prevalence -- so the self-diagnosis is poor. That's, you know, quite a generous study.

CDC is still using an algorithm for diagnosed influenza in children and did much better at improving the sensitivity but at the cost of the specificity; it's hard. The unaided clinical diagnosis has a sensitivity of about 65% and specificity of 67%. So a clinician -- which is what happens to most of these people, right now, and that's from a meta-analysis study -- gets pretty poor diagnoses. And on the right-hand side is the proposed, the FDA-proposed reclassification minimum performance guidelines as set out.

The point I'm trying to make is that that minimum performance requirement is an awful lot better than what's currently happening to the vast majority of people in the community, and that in many ways, as a minimum performance for flu, would be substantial progress at enabling these people to access a robust diagnosis.

And the last part that I'd like to put up is a picture of one of the very early pregnancy tests from the late 1960s that was in a *New York Times* article recently. The world has come a long way since this product, and it came that way incrementally by companies that invested money to make better reliable lab products that are incrementally innovated.

They did that because there was a market and because there was a realization that they could create better products than their competitors.

The point I'm trying to make is that perfection need not be the enemy of progress in this regard. And whilst we all want a perfectly sensitive test, demanding that right now might impede that progress.

That's it. Thank you.

DR. CALIENDO: Thank you.

And our next speaker is Julie Aker from Concentrics Research.

MS. AKER: Good afternoon. My name is Julie Aker. I am President and CEO of Concentrics Research. We are a contract research organization that specializes in designing and conducting testing primarily for products that are moving from prescription to over-the-counter status, or in the case of a device, professional to over-the-counter status. We work with all three centers at FDA, and we've completed 1,200 studies, 300 of which have been devices. We've also conducted test studies with diagnostic tests that are required for things such as HIV, so we worked on the OraQuick HIV home-testing kit as well as cholesterol testing kits and home drug-testing kits for drugs of abuse.

So I wanted to share the studies and development programs that are typical for these types of programs, as you consider your discussion this afternoon, and what a pathway of research might look like. The methods that are used in moving these products from prescription or professional use to over-the-counter status are well established for drugs, devices, and many of them come from either the drug side, the device side, or even from clinical trials best practices. And usually these programs are comprised usually of about five different types of studies. They aren't all needed for all programs, but there is a pathway that is established, and it usually starts with comprehension testing.

So we were listening earlier to the story that the gentleman was telling about the

colonoscopy test that was given and that one person had not been given the right instructions or had not followed them. Clearly, they had not had comprehension testing.

So usually for these programs, when we start, we start with comprehension testing because the consumer or the -- in the OTC environment, that person, our mother, our father, our sister, someone that we know -- the general public is going to have to take that device and use it themselves in a safe manner. And so the instructions that are on the exterior package, the instructions that are in the instructions for use on how to actually use the device are tested extensively in robust testing with a wide variety of consumers so that we understand if they can, if there are any areas of confusion and we can adjust that. Also, individuals of lower literacy are incorporated into these study designs.

The next type of testing that is usually done is self-selection testing, and this is done to assess whether the labeling is clear about who should be using it and who should not be using it. It is a ruling in/ruling out type of procedure.

There is human factors testing next; that is done, and this is really -- this type of testing is done to assess whether the consumer in the OTC environment can actually use the product as it's intended to be used; they can follow the instructions correctly, and they can demonstrate that they can do this.

Next, we often -- if it's a diagnostic test, we will do results interpretation testing. This is usually a two-arm type of design that has professionals in one arm and consumers in the other arm, each independently conducting the test to see what the results are and to see if they're comparable. Sometimes this is also done against a standard, and I heard discussion earlier today about what those standards should be. For the HIV testing kit that we worked on for OraQuick, that standard was a Western blot test, for example. But there was also a two-arm study that had professionals in one arm and the consumers in the other to answer the question, could consumers, in fact, use this product correctly, and could they

get a result that was equivalent to what the professional would get, if they followed the instructions correctly?

Finally, there is usually some type of an actual use trial in which the consumers are given an opportunity in a real-life environment to use the product as they would in real life when it is commercialized and available to them. This is often also done against a standard of some sort.

All the studies I just mentioned are not always required. The sponsors for these studies usually put forth the public health benefits, they discuss the risks, and then they put forth a plan to mitigate those risks through their development program. At a minimum, we almost always say that comprehension testing must be done, and we have to know that the labeling is going to be clear and well understood, even by those of lower literacy. Human factors: Can they work the device? And then also, can they interpret the results of the test? Those three studies almost always are done.

There are established guidances for these types of studies, FDA guidances. In CDER, there is a label comprehension guidance, and there is a self-selection guidance. In CDRH, there is guidance for human factors and usability that are well established.

So as you consider the development pathways this afternoon and discuss the types of studies and designs and so forth, we wanted to make you aware of the pathways that have been in existence for these programs. We look forward to the further discussion this afternoon.

Thank you for the opportunity to speak.

DR. CALIENDO: Thank you. That was very informative.

Is there anybody else that wishes to address the Panel?

(No response.)

DR. CALIENDO: Okay. Are there any questions from anybody on the Panel for any of

the speakers? Do you need more information, clarification of anything that was said? Go ahead.

DR. RAND: Yeah. Ken Rand.

I have a question. Sorry, I didn't catch the name, the speaker from Cepheid. Would your over-the-counter device have the same sensitivity and specificity as your -- as the product that you sell, you know, in hospital and commercial labs?

DR. SCHOONMAKER: Hi. Yes, that would be the intent.

(Off microphone comment.)

DR. SCHOONMAKER: That would be the intent.

DR. RAND: Would you go to FDA with a lower sensitivity?

DR. SCHOONMAKER: Let's see, what's the right answer there? We would try not to, no.

DR. RAND: Thank you.

DR. SCHOONMAKER: Thank you.

DR. CALIENDO: Natalie.

DR. PORTIS: I have a question for the representative from Ellume. You brought up a very important point when you said that you propose linking the rapid diagnostics to clinical intervention. How do you see that that would happen effectively?

DR. PARSONS: I think the actionability problem, which is one of the first questions that Dr. Hojvat wrote in our pre-submission meeting originally, and one of the key issues discussed by Clayton Christensen in the challenges of around diagnostics, needs to be solved in order for these products to have meaningful commercial uptake. So it's so what, part of the why get tested? So to be able to go and buy a test and diagnose yourself with flu is great, you know, to be able to know you have influenza. But if you still have to go and see a doctor with a positive result, sometimes therapy or a medical certificate, as many

people do, then you have only -- you've only partially solved that problem for that consumer. And in our consumer testing, there was a very clear realization that by enabling access to clinical review, the intent to purchase tests increases enormously, more than doubles.

The way that we had done that is to uniquely number each individual device which we sell and for that device number to be made available only when that -- only on a positive result. So we have single-use electronics, a little bit like the digital pregnancy tests. We have a fluorescent immunoassay that goes with that. That circuit board is numbered and on the screen, that number is made available to the consumer with a positive result. That positive result or that code is essentially a means of an externally located clinician verifying that that patient is giving a true result.

So the patent enters that code onto our website, and that's compared against our database of codes. Once a code has been used, it's crossed off the list and not to be used again, and it enables a doctor located remotely, in a telemedicine sense, to be able to have confidence in that result coming from a patient whom they are not going to know, and to be able to make a treatment decision based on, well, their clinical experience and the guidelines as per the CDC. The reason that --

DR. HENRICKSON: The patient -- without seeing the patient?

DR. PARSONS: Well, by seeing them is the same as the telemedicine providers in America currently see them, in terms of being able to talk to them or have a video consultation currently, without necessarily being able to see them in the same room as the patient, I think, would be the point there. And without a doubt telemedicine is, I think, part of the future of healthcare. Not all that much good if you have appendicitis. Reasonably good if you have an influenza-like illness and you're not in a high-risk group. So there is also no doubt that telemedicine is growing rapidly in America. And so we think that tying these

tests into a clinical consultation in a telemedicine sense solves that actionability problem, that consumers need to be able to buy tests and to put out the result of that test, positive or negative, to enable them to access a telemedicine approach to receive therapy and advice and appropriate backstop follow-up from a clinician, potentially in the case of sexually transmitted diseases a pathology request for the additional testing, which needs to be confirmed. I think this is a critical part of this program, and I think this is not only necessary for commercial success, but I think it's also necessary for the public health benefit to be realized.

One last point to make on that -- sorry, I'm taking up some time -- is that you have the ability to capture that piece of data, and I think all comers that may test in this space will look to capture that data because there will be value in it, and I think that that will be an important element of feeding through to the CDC. So I think we'll find that will be increased notifications of these important diseases.

DR. CALIENDO: Thank you.

Tom.

MR. SIMON: Tom Simon.

I guess my question would be for all of you, concerning your OTC tests, what are your recruitment outreach and awareness strategies for patients, especially at-risk populations, uneducated populations, underserved populations, and racial/ethnic minority populations?

DR. PARSONS: I'm still here, so I'll go first. So we're in the middle of running clinical trials in Australia at the minute. The studies are hard to run in terms of recruiting patients from -- directly from the community who have not necessarily presented to see a clinician beforehand. The FDA team was very clear on that in our pre-submission meetings, and we've worked very hard to design studies to achieve those goals. It has been, for us, about

selecting demographically and geographically diverse areas and about identifying -- about using means of identifying subjects that are not in a typical clinical environment, particularly for us in ILI, in pharmacies, so using pharmacies where people would walk in and potentially buy a test, to identify people with that environment and to funnel them through to the clinical study located nearby. It's not that easy, I must say. It's difficult to do. We had to work very hard and invest substantially in promoting these studies to the community to ensure that we're getting reasonable representation.

DR. CALIENDO: Thank you.

Michele, you have a comment?

DR. SCHOONMAKER: Sure. I'd like to say that we do a lot of the same processes, and both do somewhat address the question before, again. Through the design control process that manufacturers have, we create what are called design input requirements for various tests. So some of those requirements would be around test performance that, in a statistically valid population, that the performance would be equivalent to something that we already have on the market or to a laboratory test. They also involve very directed focus groups, as the previous speaker just said, with a variety of different patients of educational levels, different geographic areas. In order to meet those requirements, we do conduct pre-submission requirements to get input from the FDA as part of this process, and hold stakeholder meetings with physicians and expert panels as part of our scientific advisory process --

DR. CALIENDO: Thanks.

DR. SCHOONMAKER: -- to address those issues.

DR. CALIENDO: Julie, do you want to make a comment?

MS. AKER: I'll just add one brief comment, that for these types of programs or products ready to go into the over-the-counter environment, there's a balance that needs

to be struck between people who are not now suffering or who could tomorrow need that type of product, so more of the general population, as well as special populations at risk. And those populations are usually identified up front, and they're negotiated with FDA as the protocols are put forth. But almost always there are special populations and populations at risk that are included, including those of lower literacy. But these medical subpopulations that you're talking about are almost always included in those study designs.

DR. CALIENDO: Thank you.

Dr. Petti.

MR. WOLFF: Hi. Peter Wolff.

Just a question for Julie from Concentrics. So I think there are about 4½ million uninsured people in the U.S. Any strategies for including that particular population in any of the studies?

MS. AKER: Good point. And it does come up in all of our over-the-counter research. There's always this sense that one of the best things that we can accomplish is to have a wider access of these products, not just through the healthcare system itself. I think one of the things that we try very hard to do when we bring people into the study is we assure that we've got a very broad demographic mix. And so we're looking at those that are in inner-city areas, we're looking at those of lower literacy, we're looking at those of lower income and so forth. So we do capture those types of data, and we try to have a balance to be used so that we can represent those who might not otherwise really have access.

DR. PETTI: Cathy Petti.

In light of the pervasive use of mobile devices and smartphones, and as we all know, that market penetration has actually included underserved populations, I would very much like to hear from Luminostics, Ellume, and Cepheid, their interest in using smartphones as a platform for result interpretation to eliminate ambiguity in result interpretation for the

individual, as well as using maybe an accessory or, again, the smartphone as a platform for having consumer choice on what results should be shared, if results should be shared, to either provider or to the cloud, from a public health perspective, and be anonymous or with name or with only your location.

DR. RAJA: So my answer is easy because our product requires a smartphone to function. So I mean, this is a prototype of our product basically, right? A disposable cartridge, adapter that goes on the phone. So we use an app as the mode of reading out the test result so it makes it objective. They're not looking at something in weird lighting conditions and getting a false result.

As far as sharing the data goes, you know, that's something we're still exploring as an early stage company, but like we have a pre-submission meeting next week with the FDA, so that would probably be one thing we'd want to discuss. But the current idea is like -- the discussion today actually made me think that, like, because we're capturing this data onto a phone and we're fully aware of the security implications of -- but in terms of notifying it to the CDC, for instance, it doesn't need to have somebody's name attached, right?

So it can be completely anonymized, and we could get consent from the person that's doing the test at home and directly report it to a server that the CDC can access securely, right? So mobile security is not a hard problem in this day and age. I mean, we're located in Silicon Valley, and we have access to the experts that can help us with it. And really, like you can transfer millions of dollars with your smartphone, you know, protecting some data, like some privacy; it's not hard, right? So as far as the -- and the other aspect to this is that the mobile app component -- and this, again, is specific to our product, but I'm sure that other companies could build an app that would go with their product where the users would have to voluntarily enter information, as opposed to just directly capturing it

from the tests, where it can integrate. There are several startups that I'm aware of that are working to make a sort of cross-platform integration between an app and all of these different brands of EMRs. And so like uploading it to, like, a physician of their choice, uploading it to their electronic health record, everything -- like, those are technical problems that are easy to solve. They're much easier to solve than achieving the desired sensitivity and specificity.

DR. PETTI: Um-hum.

DR. RAJA: Right. And the same goes for the other aspects, like linkage to care. So linkage to care and notifying the CDC of these reportable infections are these two things that have been touched upon repeatedly, and those are the things that, like, with the right kind of innovation -- for us, it's built into our app and we can just do it. But, like, those are the things that are very solvable, in my opinion.

DR. CALIENDO: Thank you.

Michele.

DR. SCHOONMAKER: Hi. Michele Schoonmaker again.

There are two levels to that question. One we already have today, and that's reporting surveillance software. Our 360 software is available with our platform, outside of the U.S., to monitor in real time positive tests from our tuberculosis assay so that positive TB results and positive RIF results are automatically uploaded to public health centers around the world and they can monitor outbreaks in real time. I'm not sure how easy that is because I'm not an IT person, but that could be expanded to include things like tracking influenza and other contagious diseases. For specific devices, last year we announced the upcoming availability of our next-generation point-of-care device that will be operated by either a handheld smartphone or an iPad. We're still evaluating different kinds of platforms. We take the cybersecurity, the privacy issues, very seriously. And so those will

be pilot-tested with physician groups, with patient groups, and we're trying to work through all of those issues, but very much so we see the next generation of point-of-care devices being run with mobile applications.

DR. PARSONS: Steven Jobs's position at Apple was at the intersection of liberal arts and technology, and towards the end of his life, he came to the conclusion that a big part of the future was at the intersection of biology and technology. It's only been less than 10 years since smartphones arrived in the world, and I think in the next 10 years we'll see incredible innovation in the integration of smartphone devices into the delivery of healthcare. I think that's a certainty.

The hard bit is creating biological interface, to create -- take a piece biological information and create a piece of digital data out of that, and then to make that piece of information useful and robust and of value to the consumer such that they are prepared to pay for it. So the opportunities are really limited only by our imaginations in solving those problems. Certainly, our subsequent products will be products that link very closely with smartphones, and we see that as a natural, important way to continue to innovate.

DR. CALIENDO: Lizzie.

DR. HARRELL: Lizzie Harrell.

For Ellume, I had a question -- I have a comment and a question. First of all, I wanted to say I think your comment about using telemedicine --

DR. CALIENDO: Lizzie, can you speak --

DR. HARRELL: I'm sorry.

DR. CALIENDO: -- into the microphone?

DR. HARRELL: I think your comment about telemedicine is very forward thinking because there is so much of medicine going in that direction right now. But the second one had to do with a comment you made about sensitivity of tests. I'm not sure if I got your

quote completely, but you said we want a sensitive test, but that may impede something. I didn't quite --

DR. PARSONS: That perfection might impede progress.

DR. HARRELL: But if we try to have a very sensitive test, that was going to impede the -- did you say that was going to impede the development? I couldn't get the rest of your comment.

DR. PARSONS: Yeah, sorry. The point I was trying to make was that in discussing the minimum performance requirements for these products, it is -- it's very easy to understand how, from an individual perspective and from a community perspective, having high performance requirements is obviously in the best interest. And you know, I think we would all like to have very high-performance products. I will say, from a company that's really lived through that development now for some years, it's hard.

Making home-use products that are -- well, that are simple enough for the average person to use in middle America who didn't go to high school, to get it right the first time with no instructions, and to make it safe so that the risk of harm from using the test is essentially zero, to make it accurate, particularly sensitive enough that the risk of false results is low enough to be acceptable, to make it actionable so that that result can -- you know, it can lead to actually solving the problem that consumer has, and then to make all of that affordable.

You know, we've been talking of the $10 to $20 range. You know, so bear in mind, you know, you buy something for 20 bucks in a pharmacy, the manufacturer is selling it for 10 or less, and the cost of development of these products is substantial. The cost of these studies is substantial. That means you've got to be able to make it for less than 3. It's pretty hard, it's pretty hard. So if we set a bar of saying, you know, these tests need to be in the high 90s in performance, then achieving that will be very difficult. Getting the cost of

molecular to be somewhere near that will be very hard. I think -- sorry. In the future, the future is definitely molecular, but I don't think -- I don't think the world is there yet, from what I can see, in making that affordable. The point I was trying to make is that it's easy for perfection to impede progress.

DR. HARRELL: Thank you.

DR. CALIENDO: Okay, I think we're going to move on with deliberations. So we will now resume Panel deliberations from this morning. 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 everybody to introduce themselves before they speak. Turn your microphones off when you're done speaking. We're going to open up the floor now to questions for the FDA, guest speakers, and the open public speakers. But before we do that, Dr. Tamara Feldblyum is going to read the FDA questions to help the Panel focus on what the FDA -- the specific questions that the FDA has asked us.

DR. FELDBLYUM: I am a Branch Chief in the Division of Microbiology Devices, and I will present the questions to the Panel. First of all, I would like to thank the Panel and all the speakers for all the work they have done so far, and we expect much more to come this afternoon. The questions that I am about to present will sound familiar because many of these topics were brought up already by our speakers and in preliminary discussions, and I would just like to ask the Panel to please consider every question in regards to the specific pathogens that we addressed this morning because the answers for each pathogen may differ, depending on the benefit and risk profile. So we have five questions to the Panel.

The first question is: Do you agree with the benefits and risks described for over-the-counter testing of each of the pathogens, and are there any other benefits or risks that should be considered?

Question 2: What measures would be appropriate to mitigate the risks associated

with over-the-counter diagnostic testing?

Question 3: What would be the recommended minimum performance criteria for testing of each pathogen? And that concerns influenza, chlamydia, gonorrhea, and strep that we discussed this morning.

Question 4: Please discuss recommendations for ensuring that individuals representing the appropriate intended use population are enrolled in the clinical studies to demonstrate the device performance and support over-the-counter claims.

And the last question, Question 5: Please discuss appropriate ways to connect patients to healthcare services.

a. Are there any recommendations regarding potential patient access to additional resources that diagnostic test manufacturers should be responsible for (e.g., a hotline)?
b. Does this differ across the diseases described above?

Thank you. And we look forward for deliberations.

DR. CALIENDO: Thank you.

So what we're going to do is we're going to have open discussion, and then we'll come back to these questions, and each Panel member will be asked to comment on each question. Before we start, let me just remind people to keep our thinking general. You know, the discussion this morning just kind of focused on do we think antigen tests are kind of a dog and we think molecular is good, but that's today, and we don't really know what's brewing. And so when we give recommendations, we don't necessarily want to recommend a specific test as a gold standard but maybe the performance of the test that we're looking at. I think we need to keep it general because we don't know where this field is going to go. When we were sitting here 10 years ago, we wouldn't have necessarily predicted where we are now. So that's just a piece of advice as we talk through. So now you're free to ask

questions to anybody who presented to us so far. We can just talk through issues as they come up.

DR. VAN DER POL: Barbara Van Der Pol.

I just want to reiterate something that was said this morning because I think it's really critical to all of our thinking, and that is that for the chlamydia and gonorrhea, so not necessarily flu, but for chlamydia and gonorrhea, remember that over-the-counter tests are not going to replace the status quo. And so when we're talking about benefits and we're talking about risks, I think that when we make comparisons like, for example, what if people had a positive result and didn't get it treated, the comparison is not to them not getting treated because they had this positive, but to them not having gone to the clinic that is part of the status quo. And so I think we have to really put the benefits in terms of an additive increment. And I think that's a really critical difference than thinking that we're moving away from one paradigm to another, but rather I think we're adding a second tool to our toolkit.

DR. PORTIS: On that front, a question for the clinicians in the room, that with this added step -- let's say that these tests are approved and they're necessary -- would the clinicians in the room still want to re-perform the test? How would you, as clinicians, deal with that when someone calls and says, oh, I have this positive test?

DR. CALIENDO: So Angie Caliendo.

So I think it's a really important question. It's something that came up a little bit this morning, and I think that's going to be driven by the expertise of the physician, the understanding that any individual clinician has of the test, the confidence that they have in that test will drive that decision making. And so I think it's going to be very difficult to just say, across the board, what physicians even should do with a test result. And that's what makes it challenging. If we're going to bring everybody back into a doctor's office and

repeat the test, we have defeated the purpose of -- a portion of the purpose of what we're talking about. I think what Barbara has said is important, that we shouldn't view it as black or white or a replacement. It's another tool that we're putting out there to get people into care.

DR. RAND: Ken Rand.

I think physicians would respond very positively, but I think you would have to have secure information systems, and I think that would be key, information systems that the patient was the patient and that the test result they saw when they went to the website or app on their phone was, you know, protected and secure. I think there would be physician acceptance. I mean, after all, ultimately they're going to be from the same generation as the patients.

DR. HAMMERSCHLAG: Maggie Hammerschlag.

However, there's one other aspect. When you've identified an STD in somebody, you mean that they probably have to be tested for other STDs, some that may not and probably will not be available as over-the-counter tests. So that may be another reason to go back to see a physician if you're positive, not so much to get that test confirmed. That would very much depend upon the performance parameters of that particular test, and we'll hopefully have that information. The other point would be that they would need to be tested for other things, especially something -- maybe syphilis or *Trichomonas* or whatever is available.

But also they, at least early on, provide maybe some mechanism to have some kind of surveillance of the continuing performance of the test, I mean how it performs, because with the FDA now, there is for drugs postmarketing surveillance. If they begin to see adverse effects, it's reported as a mechanism for that. If this test goes out there, what kind of mechanism they're going to have to determine that it's performing the way it's supposed

to perform, because we do know these companies will change formulation. You know, there are tests that are no longer on the market because of a variety of problems, drugs that are no longer on the market. Telithromycin, anybody? And this may provide at least maybe -- it has to be somehow, I think, built into this.

DR. CALIENDO: Cathy.

DR. PETTI: Yes, I just have a question for Drs. Gitterman and Scherf before we go into greater deliberations about this issue. I would appreciate some guidance on when we're looking at performance characteristics, do we couple or decouple performance characteristics of a specimen collection device from the diagnostic assay, or do we think of it as one system?

DR. SCHERF: I'll take this one. From our perspective, it's actually very important to view this as a system, yeah, where you have the opportunity to obtain the sample and then do the testing. We know this is more challenging, but at the end of the day, it's really important from the patient perspective that you obtain the sample and you obtain the result. What happens in between, of course, we will look at it, and we evaluate it the appropriate way, but we will never separate it from each other because it will open up too many combinations of maybe, then, unmanageable scenarios that will not benefit the public.

DR. CALIENDO: That's helpful. Thank you.

Other questions or comments?

DR. DODD: Yeah, I just wanted to follow up on the --

DR. CALIENDO: Introduce yourself.

DR. DODD: Lori Dodd. Thank you.

I want to follow up on the comment about this just being an additional supplemental kind of test. What happens when the test is a false negative and therefore I don't go in for

my regular visit and don't get the test, or I don't go in and see my clinician when I think I have the flu because my test is negative, so I get a delay in treatment for any of these conditions? So I think we have to be very careful when we think through the issues because it's not necessarily just an add-on.

DR. VAN DER POL: Well, I think that's one of the reasons I tried to be really clear up front. I was talking about STD and CT/GC in particular and not flu because I think there are really big differences. But the piece about the STDs that concern us are the number of people we're not reaching because they are asymptomatic. So if they're asymptomatic and they do -- and they weren't going to go in to the clinic but they opt to take an over-the-counter test and that over-the-counter test is positive, we're no worse off than we were because they weren't coming in to the clinic. We may be better off because, as they perseverate on that, they may decide, oh, really, I do have to do something. And so it still may be a cue to action, we hope it will be a cue to action, but even if it's not, at least that individual is informed, and that's a step ahead of where we were when that individual wasn't accessing care.

DR. HENRICKSON: Unless it's a false positive.

DR. DODD: Yeah. Well, I guess my concern is what if it's a false negative in that case, and I think, oh, I'm no longer at risk, I'm clean, I don't have any STIs.

(Off microphone comment.)

DR. DODD: Well, but I mean maybe it gives me a false sense of reassurance, and I'm less likely to go in and get checked up.

DR. CALIENDO: Angie Caliendo.

I think that's true, and I think, Lori, that's the risk, and you have to weigh that against the benefit of what Barbara is talking about.

DR. DODD: Right.

DR. CALIENDO: I think we've laid both of the issues on the table, and the question is how do we mitigate the risks so that we can reap the benefit?

DR. DODD: Right. I just think you need to keep --

DR. CALIENDO: And that's kind of what they're asking us.

DR. DODD: -- both in mind, and it's key to understand operating characteristics of the diagnostic --

DR. CALIENDO: Yeah.

DR. DODD: -- test, right?

DR. CALIENDO: Yeah.

DR. GAYDOS: At the end of the day, it's all about weighing the risk and the benefits.

DR. CALIENDO: Introduce yourself.

DR. GAYDOS: Or, you know, is the need significant enough that by offering these over-the-counter tests, we're going to get more people treated? And I think one of the things that we have to -- that we haven't talked about too much with the benefits -- we talked a lot about the risks. One of the benefits is it's an opportunity to educate, and if someone goes to the trouble to buy the test, they're spending money and they do the test, and whether it's right or wrong, it's still a chance in that kit that they buy to enhance education, to get them to think about maybe I should just go and get this double-checked somewhere.

So the opportunity to self-empower people to think about their own sexual health or their own respiratory health during the respiratory season, I think, is one thing that we can't eliminate or can't gloss over because, again, you know, it took us years to educate women to get Pap smears and to get their mammograms, and it's baby steps along the continuum. And I think this has to be carefully monitored.

MR. KIMES: Yeah, this is probably more of a comment than --

DR. CALIENDO: Introduce yourself.

MR. KIMES: Oh, sorry -- Dave Kimes -- more of a comment than anything else because of, you know, the dynamics. And if we have a scenario where -- you know, how to run the device, how to collect the sample is really important. You can encode that device so that in order perhaps to run it in some way, you have to log on to a website to be able to get information and get training videos, all the positives that we've talked about potentially. You know, now, that might be a little bit harder in the self-performing scenario, but you know, there may be some mechanisms to put some levels of controls in there to help increase the positive predictive value of these devices.

MR. SIMON: Tom Simon.

I guess to direct this to the physicians mainly and maybe the OTC providers, does the liability factor raise its head in any of these discussions and any of these items? And how would a physician address that? How would the OTC address that? Is there any liability that you would worry, you would consider that would make you go one way or the other?

DR. CALIENDO: Steve is looking at me.

(Laughter.)

DR. CALIENDO: I would be Angie Caliendo.

You know, from a clinical perspective, I mean, I think it's no different than any other test that I run that I have to interpret and make a decision on. I don't know if it's different for the manufacturers. I would be curious to see their perspective, and I don't even know if the FDA considers that in their thinking.

DR. GITTERMAN: No, we don't.

DR. CALIENDO: So I don't know. I would ask whether from the manufacturers' perspective as to how you guys assess liability.

MR. KIMES: Yeah, I guess that's a complicated process, but you know, at the end of

the day, you know, with the quality system controls we have in place, that helps guide us through a robust design process. So, you know, I'm more in the Class II side of things with these devices versus a Class I scenario because of the rigors that that brings to the table. And as long as you have those rigors balanced with strong scientific evidence, because nothing's perfect -- you know, biologics are not black and white -- then you've done what you've needed and you're maintaining the device on the market where it meets its design specifications.

Now, if you market a device that's below its design specifications, then you're liable. You know, so you have to kind of -- you have to be behind that. It's kind of the same place that FDA is in. I approved it at this rate. I don't have maybe a way of taking if off the market unless it performs lower than it needs to. So I don't know if that answers the question, but that's, you know, how we look at it.

DR. CALIENDO: Go ahead, Charlotte.

DR. GAYDOS: One thing that I think --

DR. CALIENDO: Charlotte, please introduce yourself.

DR. GAYDOS: Charlotte Gaydos.

I think one thing that we have to remember is that there's an advantage of marketing and packaging in that we can make sure that consumers, as we all -- laboratorians always tell their clinicians no test is perfect. We're never going to have a perfect test. And there should be plenty of instructions in any sort of a home-use kit that tells the individual that, you know, these tests are not infallible and that if they're symptomatic or they perceive that they still might have an infection, they always have the option of going in or having the test repeated. So I think there are things that we can do to mitigate some of the risks that we talk about with packaging and educating.

DR. VAN DER POL: Barbara Van Der Pol.

Another thing I just heard and I want to -- I don't think anybody's really touched on today, Cathy mentioned use of smartphones and the fact that smartphones had really become, you know, the predominant communication tool, even in disadvantaged settings, and that's very true, more so overseas probably than here. But even so, here, the vast majority of people have smartphones. I would say that it's not necessarily true that they have data access and that they have Internet access. So when you're talking about solutions that rely exclusively on the Internet, I would caution us that if we're really trying to reach out to those people who don't access healthcare and they're underserved in general, we don't want to rely on the Internet too terribly much.

DR. HENRICKSON: Kelly Henrickson.

DR. CALIENDO: Kelly.

DR. HENRICKSON: Oh. I just want to reemphasize how different what you're -- the sexually transmitted diseases are from the respiratory illnesses. And again, you care about asymptomatic. You hope asymptomatic teenagers will test themselves, and we hope asymptomatic people won't test themselves.

(Laughter.)

DR. HENRICKSON: And so there's a whole different public health mission that I think has to be involved in the discussion.

DR. CALIENDO: Go ahead, Maureen.

DR. BEANAN: Yeah, I just wanted to comment. Maureen Beanan.

I just wanted to comment on Internet access. And the Pew Research Foundation has done a study in 2015 saying that, on average, approximately 90% of Americans use the Internet, 78% African American use the Internet, and 81% Hispanics use the Internet.

DR. VAN DER POL: But a lot of those people use the Internet at the library, and that's not going to be terribly appropriate for walking you through a self-collected STD test.

(Laughter.)

DR. PORTIS: I know we're going back and forth about that issue, but I think it's an important one because I think it's easy to assume that everyone has access, and I know and work with a lot of people who do not have that access. Oh, Natalie Compagni Portis. Sorry, no introduction.

And so, as our speakers pointed out, it is a brave new world, and we have to respond to that, and it's this new paradigm, and in some ways, that makes me want us to be very cautious as we go forward, to really understand all of that and understand the access issues and not make big assumptions, and in the research, to not leave out these big sectors of the population who continually do get left out of these assumptions.

DR. CALIENDO: Angie Caliendo.

But you know, Barbara has said this multiple times today, and I will say it again, they're already being left out, and are we doing any harm if they don't come in but we get other people in? And I think that's kind of how -- we have talked a lot about the risks, but I think there are benefits that we need to recognize. We'll never catch everybody, but my gosh, if we catch some more that we wouldn't have caught, I think that's how I'm framing, at least in my own mind, the benefit.

DR. HANSON: Kim Hanson.

DR. GAYDOS: Charlotte Gaydos.

DR. CALIENDO: Wait, hold on.

Kim.

DR. HANSON: Sorry. Kim Hanson.

And I would say it almost needs to be a multimedia approach. There's print educational materials, there's Internet and videos, there's texting, there's hotlines you could call. It seems we need to get creative to find ways to -- you know, people learn in

different ways and to try to address that.

DR. GAYDOS: Charlotte Gaydos.

And the Z generation, at least the STDs are in the younger generation. So being creative and bringing more in has just got to be additive. We wouldn't see them otherwise. And so as diagnosticians, we need to respond to social norms.

DR. RAND: Could the FDA -- does the FDA make its decision to approve an OTC device based on the characteristics of the device, say, sensitivity/specificity per se? Or the requirement for interaction between the results of that testing and the healthcare system; could there be a requirement for some sort of communication there, in addition to just the performance characteristics of the device?

DR. GITTERMAN: This is Steve Gitterman.

Of course there could be -- of course there would be requirements regarding a minimal performance, of the sensitivity and specificity, as appropriate for the test as opposed to appropriate for the clinical scenario. Intuitively, I cannot see any way we could require somebody to go to a physician or -- you know, or have that contact as a product of the device. I'm not quite sure how we would enforce it --

DR. HENRICKSON: Well, I have a suggestion. What if --

DR. CALIENDO: Introduce yourself.

DR. HENRICKSON: I'm sorry. Kelly Henrickson. Sorry.

What if, for example, like flu, where I'm more concerned, you actually have -- we approve devices that only will give you the results through a contact with a healthcare professional? Or get a telemedicine kind of contact.

DR. GITTERMAN: Again, I'm not quite sure that -- well, there's a lot of pragmatic concerns with that, how that would be done, you know, the expectation on the sponsors to do that, what you would do with -- you know, there's a million pragmatic concerns with

that. I'm going to get -- yeah. Thank you. I'm getting some advice here.

(Laughter.)

DR. GITTERMAN: But again, you know, the bottom line is, is the test safe and effective for its proposed use? If it cannot be used safely and effectively without some type of physician contact, I'm not quite sure -- and again, I'll welcome the discussion. It could be an OTC test in that regard, if you think that contact with a physician or a health professional is absolutely essential.

DR. HENRICKSON: Well, we've heard today about how the world is changing and how we need to be able to have people be able to get the tests. So I can imagine a world where -- or I can imagine a world where there are illnesses like influenza where an over-the-counter test can be performed safely, perform safely, but where the interpretation of the results is what is actually needed by a healthcare professional to determine whether treatment is appropriate, and I mean where the public health is only improved by the contact with a physician.

Not that it's not a very sensitive and specific test, but actually over-the-counter tests have not been -- maybe we'll have studies that show that the public health is not improved by over-the-counter tests that are 100% sensitive and specific unless there's a contact with a physician to determine whether treatment is appropriate, to help encourage them to stay home, because they won't stay home, and I mean all of the public health benefits may only occur with that contact.

DR. GITTERMAN: Right. I not saying theoretically -- this is beyond my expertise -- to say can we have a special control which would say that you could only use this test if the test -- you know, put this on the sponsors and say there has to be a built-in mechanism that you can't possibly get your result without some type of contact with a physician. Pragmatically, I think it might be a little rough, but I would have to investigate whether

that's an option. I suspect not, that we could possibly do it, and I certainly would look at it.

DR. CALIENDO: Go ahead, Uwe.

DR. GITTERMAN: Some of the manufacturers may want to comment.

DR. CALIENDO: Go ahead.

DR. GITTERMAN: Please. But I --

DR. SCHERF: May I?

DR. GITTERMAN: Please.

DR. SCHERF: Yeah. So just Uwe Scherf adding on to Steve's comment. I think what is doable, if some of these activities you just described is mitigating the risk, yeah, then FDA can make the argument this is essential of being part of the device. But as you already see, it will be very, very challenging to put this into a wording or into a descriptive kind of a sentence or a recommendation. But if you are mitigating the risks, then the opportunity is, from our side, to actually to do that.

DR. CALIENDO: Great, thanks.

Kathleen.

DR. BEAVIS: But I think we have to keep in mind, too, the difference -- you know, in the Executive Summary, two kinds of testing were described, one where the person collects it and then mails it off or gives it to someone else for interpretation, and the other, the totally self-contained testing that I thought we were supposed to be describing here today. And if we start putting all of these conditions on that, say, well, you have to send a code in to somebody to get the answer, well, we've moved away from the test that I think we're supposed to be evaluating. My other concern, too, is that for better or worse, I think one of the biggest advantages of over-the-counter STD testing is the anonymity that that gives. And I think if one of the conditions of getting an answer, that all of a sudden you're plugged into the health system, I think some of those benefits go away.

DR. SCHERF: Absolutely.

DR. BEAVIS: Thanks.

MR. WOLFF: Hi. Peter Wolff.

For several of the studies that I have run or that I have managed on STDs, one of the biggest problems that we hear is the amount of time required. People don't want to spend more than an hour at an STD clinic getting diagnosed; if you have an OTC, you can get a diagnosis in minutes. Then you have the marginalized patients. You know, what about the mom that has five kids and has to stay at home and doesn't have, you know, a couple hours, or someone who's got, you know, a 9-to-5 job, they can't take an hour off from their job to go to the STD clinic. So I think OTCs are definitely needed, and I don't think they should be held to the same high standards that NAATs are right now.

DR. NOLTE: Rick Nolte.

So this may be completely off the wall, but these are going to be FDA-cleared over-the-counter tests, and they'll be performed by patients, and they're going to presumably act on that information through an interaction with the healthcare system. So is this going to involve -- I mean, how is this going to play with CMS? And what happens with -- you know, if another test has to be performed? And, you know, we're all moving away -- supposed to be moving away from fee-based, you know, reimbursement and outcomes are important. So I know this is going to be a glacial process with the FDA.

(Laughter.)

DR. NOLTE: I mean, I was on the 2013 Panel for the influenza, and we're not any closer there. But those are things that are changing, and I just don't know. This is a new paradigm for me to think about, but I just wonder whether it does have any ramification in terms of insurance providers or anything like that. I mean, are you going to have to get a real test to get the patient's insurance company to pay for the Tamiflu or --

DR. HENRICKSON: We're not supposed to be contemplating costs and money issues here.

DR. NOLTE: Oh, okay.

DR. GITTERMAN: Yeah. I have to say perhaps you could flesh that out. This is Steve Gitterman again. I mean, if I got to get a pregnancy test --

DR. NOLTE: Huh?

DR. GITTERMAN: If I were to just to go get an over-the-counter pregnancy test, I don't think I'd worry about CMS or many other issues, and especially, let's say, if the test was negative, I certainly wouldn't worry about calling an obstetrician.

(Off microphone comment.)

DR. GITTERMAN: No. No, but you'd have to flesh it out, but I do worry that this may be beyond the scope --

DR. NOLTE: Okay.

DR. GITTERMAN: -- of what we're talking about. I mean, to the most reductionist, certainly we could talk about benefits or risks and ways of mitigating that risk. But in the simplest case, you have a test, you look at the result, and you decide how to follow it up. And again, not to go back to your example before of requirements, but I think everybody has said that education is a huge part of it, and having the availability of resources and whether you're talking about videos, you know, online available consultation, whatever.

But you know, the issue of CMS and some of these other issues may be out of scope unless you truly feel that without some type of required follow-up, then the test would not be safe, and then I would certainly question whether it's simple and easy enough to use in the outpatient setting -- and we took that back, you couldn't say that it's -- if it's really not independent at all of the healthcare system, it may not be, you know, safe enough to use as an OTC.

DR. HENRICKSON: Kelly Henrickson.

Again, that gets back to the analyte. One is a pregnant person, and the analyte is the baby, and the other is a sexually transmitted disease or again -- or a respiratory illness, and they're so different that we keep talking generally about controls and the assays, and I think that -- I think for each analyte, whether it's a baby or a sexually transmitted disease, first, the FDA or the Panel has to decide what is known about what it will do for the public health, and I think that that's -- I just keep coming back to that because, again, I see very different outcomes for sexually transmitted diseases that seem like over-the-counters have a natural place, and I'm worried that we don't have enough data or studies that demonstrate what would happen if millions of people got tested for flu over the counter, and what would happen to flu with antiviral prescriptions, what would happen to -- you know, whether the public good would be improved.

DR. NOLTE: Can I just follow up to your analogy with the pregnancy test? And forgive a naive question. So if a woman goes to her obstetrician and says I've taken a home pregnancy test and I'm pregnant, does the obstetrician do a lab-based test then, or do they accept the --

(Off microphone comment.)

DR. NOLTE: Huh?

(Off microphone comment.)

DR. NOLTE: Yeah. So yeah, there goes the --

DR. CALIENDO: Pregnancy is kind of a bigger -- Angie Caliendo -- kind of a bigger deal than the flu. You know, it lasts a longer time and more --

(Laughter.)

UNIDENTIFIED SPEAKER: It doesn't stay asymptomatic.

DR. CALIENDO: It impacts your life a lot differently.

DR. GITTERMAN: This is Steve again.

Just two points: One is I completely agree. As to the point -- well, first of all, I agree with both your comments. I better speak louder. The first case was discussed earlier this morning. It depends on the risk-benefit and the components of the device. We have group A strep tests which are so sensitive right now that the package insert does not recommend doing confirmatory tests, that the performance is felt to be high enough, and we've done internal statistical models to say you don't need to do it. So again, whether somebody who comes in -- you know, it depends if you want to do a confirmatory test is really going to depend on the physician, if you're comfortable with the test, the individual involved, a lot of reasons. But I think as we've all said -- and again, well, whether they even come in if they don't have a positive test is a potential risk of the devices.

The second thing is that's why we have you guys here. I'm using "guys," you know, to the group. But if somebody could do that million-person test of what if we did, if we had -- you know, if we did an OTC out there and what would happen -- that's not going to happen. The problem is, you know, without a test out there, we can never do the test, and we can never do the study to know what the effect would be unless somebody funded it. So it's a difficult question, and I have to say that really is one of the major reasons for bringing the group together, you know. Assuming that they've, you know, demonstrated all these analytical characteristics, do the benefits and risks of the test outweigh it? And I don't need to speak for the entire Committee.

DR. CALIENDO: Okay. So Barbara and then Mark.

DR. VAN DER POL: Barbara Van Der Pol.

So one of the things, though, that Kelly just said that I think is also really relevant to this: While I'm distinguishing between CT/NG and respiratory or flu, I would also say not all STDs are created equal. And so whatever determinations we make here that may be

relevant to CT/NG may not apply to syphilis, may not apply to herpes. And so we need to be really thoughtful. Within that field we're still a broad can of worms, and so we need to just know that we're going to have to some fluidity and flexibility.

DR. MARTENS: Mark Martens.

Two comments: First, when you mentioned the point-of-care testing, they have to be quick because people are busy. The home test doesn't have to be quick. You know, I think if we're going to do some amplification, it may take a while longer. So for their home, it doesn't matter if the test is 20, 30 minutes, although people get bored and want the test results.

(Laughter.)

DR. MARTENS: You know, the people looking at the pregnancy test and want to know what's going on at that second. So it doesn't have to be quick. At point of care in the office, they don't want to sit there for an hour to 2 hours.

The second point. The pregnancy test is a good example, but it highlights the risk, although I'm all about the benefits. But when as Director of Planned Parenthood in Oklahoma and Arkansas in the past -- and you besmirched Oklahoma earlier -- what happens when a patient comes in and we do a pregnancy test? If it's negative, that's the opportunity that we have to say why do you think it's positive? How come you're not using birth control and prevent the outcome they don't want? And you lose that with a home test, unless there's extra educational value, which you can do.

DR. GITTERMAN: Right. I have to say -- and this is Steve again. Again, giving credit to Gina when she was giving the background, just buying the test -- and I don't know if I'm disagreeing or agreeing with you -- has educational value because you could have the negative result. So I hear you, but I think in our deliberations, sometimes even being able to test and then have the access in the device, whether it's Internet or whether it's video or

whatever, conceivably has educational value. So I agree, it may not drag them in to be there in the physician's office.

DR. MARTENS: No, but you add something that says, you know, even if the test is negative for STD or for something else, your concern should bring you to, you know, find and get more information, go on the Internet or see your healthcare provider.

DR. GITTERMAN: Absolutely.

DR. MARTENS: So just to try to get to our questions, the -- generally, we're worrywarts. We worry about the risk. You know, most of us took the oath, don't -- do no harm. But as you said earlier, we've got to move forward, and I think the benefits outweigh the risks. I was totally against the over-the-counter morning after pill. The teenage pregnancy rate is going down, you know, and -- you know, I was against yeast medications going over the counter, you know, but millions of women have saved, you know, hundreds of millions of dollars from not going to the doctor's office.

So I think the HP vaccine I was for, but there are a lot of concerns that it would make all teenagers promiscuous, as if they weren't already, but -- and it's not -- the Pap smear, abnormal Pap smears are going down, cervical cancer rates go down. So I think, you know, we tend to look at the risks, and that's probably our job, but I think the benefits outweigh the risks. When we get to the questions later, I think I agree with Barbara, I separate influenza and group A from GC and chlamydia. But I think they're all beneficial.

DR. CALIENDO: Go ahead, Lizzie.

DR. HARRELL: Lizzie Harrell.

I was just going to make a comment. We haven't talked a lot about group A strep as far as the positives about having over-the-counter tests. When you think about young mothers and they have children going to school, if you have a test out there that they can get up in the morning and somebody has a sore throat and you can do a test and call in

some -- have the doctor call in some antibotic and have the child start it then, rather than the mother being out of work for a day trying to get everything together to get that child tested, that may -- I could see that as being something that young mothers would probably like to have. And others, too, but I can see that as being something that I know a lot about as far as children and trying to get --

DR. CALIENDO: Okay.

DR. HARRELL: -- group A strep diagnosed.

DR. CALIENDO: Lori.

DR. DODD: Yeah. Can I ask the clinicians in the room to expand on that a little bit? So, for example, my pediatrician won't even take a nighttime pediatric test result because he doesn't believe they know how to run it right. So he always wants to see my kids and make a clinical assessment about whether they have strep or not. They rerun the test. So I mean, my understanding through my own personal experience is it's a conglomeration of symptoms, and maybe the diagnostic accuracy is high enough, but does it actually -- is it high enough to trigger action? And so, you know, are we going to send the wrong message by taking away that clinical judgment in the process? I mean, that's one side. I mean, obviously if it's triggering people to go in and see the clinician, I think I'd feel differently about it. But if we're taking out that clinical judgment piece, are we doing a disservice?

DR. HENRICKSON: Kelly Henrickson.

The majority of sore throats in children are not group A strep, the vast majority. So it all gets down to sensitivity and specificity and false positives and false negatives. So the vast majority of the time when your child wakes up with that sore throat and you swab them, if the test is highly specific, it will be negative. But I guess that's the answer. And if it's positive, then the only issue is how often is it false positive, since most of the time it's supposed to be negative. But I mean, that is true of whether it's at the doctor's office or at

your house. If we can get over the collection issues and we set, again, good sensitivities and specificities and special controls, then all of that can be handled. And what your doctor actually sees in the office doesn't help very much, just so you know. I mean, as an infectious disease doctor, I can tell you that, you know, if they're big, red, swollen, and pussy, which is not very often -- excuse me. But most of the time it's just a red back-of-the-throat. And you could over the phone tell them, hey, I looked in the throat, and it's all red in the back. So the clinical diagnosis of strep is very difficult clinically.

DR. CALIENDO: So I'd like to get to a point -- sorry, this is Angie Caliendo. I'd like to get to a point that we're going to have to advise the FDA on, and that is what level of performance. And we've been tiptoeing around it a little bit, but maybe we should talk about it for a little bit and then talk -- after we finish that, talk a little bit about specific special controls. And so what is the sensitivity and specificity of an over-the-counter test for chlamydia and GC that is acceptable? I think we need to bat that around amongst ourselves. I've heard it doesn't have to be as sensitive. I've heard, if you make it as sensitive, you'll slow progress. I've heard don't you dare put a dog of a test on the market. So what is that sensitivity and specificity? Can we have a little chat around that to see where our heads are with that?

MR. KIMES: Again, can I take a stab it? Okay, so you know, the first thing with any diagnostic test is to inform clinical decision making, period. So you can't leave the doctor out, especially on a positive result. And I think that's, you know, absolutely critical. So in the context of that and in progress, because we don't have perfection, I think these tests need to be somewhere between where they are today, you know, the over-the-counter tests with not as good specificity, but they're not going to be as good as a PCR and NAAT test, and it's got to be somewhere in the middle of that to be able to benefit. Then we have to look at it and say, okay, going back to the risk-benefit, will the overall risk-benefit

advance patient care so that we are treating more people in a positive manner? The negatives are important because it reduces anxiety when they're accurate; I know I don't have to go to the doctor. And when it's positive, I have to get treatment; so yeah, I have to go to the physician. You know, to me, I think it's somewhere in there, because we're not going to come up here and say, hey, it's got to be 98% specific and you know, 90% sensitive. That's going to be too hard to do. But in generalities, I think it needs to be somewhere in the middle so that we can get that positive outcome for our patients.

DR. CALIENDO: Okay, Barbara and then Charlotte.

DR. VAN DER POL: I disagree completely. Sorry.

(Laughter.)

DR. VAN DER POL: There's no reason we have to settle now. The technology is here. We have amplified diagnostics for chlamydia and gonorrhea that will be available in a format that could be used over the counter, if we choose to, within the next 2 years. So by the time we finish this process, those assays will be ready. And we could argue that we could take lower sensitivity because there have been a lot of economic studies done showing that in certain populations you actually treat more infections, and so there's a public health benefit. But when we know that there are technologies that will allow us to have tests that are just as good, why shouldn't we ask for that?

DR. GAYDOS: Charlotte Gaydos.

We're not going backwards. The technology is there to have the same sensitivity that the FDA requires for NAAT tests. And if it takes an over-the-counter NAAT test to meet that sensitivity, those technologies are going to come. We don't want to go backwards when we're trying to go along the pipeline to get better and better assays. And I personally don't think the FDA should ever recommend going for less sensitivity or less specificity than what they require for laboratory tests right now, because I think it's achievable.

DR. CALIENDO: Go ahead, Ken.

DR. RAND: Ken Rand.

I would certainly agree with that. I mean, we've got -- you know, the standards need to be as high as what's available if they go into the healthcare system, you know, within a few percent. But if it isn't -- if you're going to start approving tests with less than 90% sensitivity, I think that's a disservice. And if you want to put numbers on, I would be over 95% sensitive and over 90% -- 95% specific. And if you do the math, as you all can do in your heads, for the problems of low prevalence with those numbers, you know, that's a compromise.

DR. HENRICKSON: Kelly Henrickson.

Unless something's changed since last time I submitted a 510(k), you guys don't say it has to be 99%.

(Off microphone comment.)

DR. HENRICKSON: I mean, you allow -- used to allow, you know, 95 percents and 97 percents for NAAT tests.

DR. GITTERMAN: Right. Well, the CLIA waiver guidance has a specific number in there, 95%. But in fact, it also has the proviso that if it's clinically -- if there's a clinical justification that's a wider performance that you observed or planned, was observed and you can justify it, then in fact we would allow a lower number. And I think that's the discussion we really want to appreciate because, again, I think we've heard the view that the population may benefit overall by having greater acceptability, as would be the HIV case, which I would notice took three -- I would, you know, note took three Advisory Committees and probably years of discussion to come to a conclusion. However, I think we've heard the other approach since. And you hadn't mentioned this at all. We can't do the million-person study to say do we gain by getting more of the people who wouldn't

come in, you know, otherwise versus having the people who may be very well off, who will use the test for convenience because they don't want to lose a day's work, yet the diagnostic performance isn't as good. It's a difficult issue, and you know, there's many counterbalancing -- there are many counterbalancing points of your perspectives. So again, that's why we look to you as hopefully experts.

DR. CALIENDO: So Angie Caliendo.

So anyone else have thoughts on GC and chlamydia because -- go ahead.

DR. VAN DER POL: Well, we're all just kind of arbitrarily throwing out numbers, but I actually would like to say that what I really think is best is if we hold them to this essential equivalency, right? So we want to say that these things are substantially equivalent to the lab-based NAATs. So I'm not trying to pick a number, I'm not trying to say we have to hit a number, but if there is something on the market that's already been approved and that's acceptable in-lab settings, that's the benchmark I'd like to see.

DR. HENRICKSON: Kelly Henrickson.

To be specific, it's only the CLIA-waived that have that 95%.

DR. GITTERMAN: Yes, sir.

DR. CALIENDO: Yes, but --

DR. HENRICKSON: So lab-approved tests. I mean, people might not use them because most NAATs are in the high 90s, but lab-approved tests that aren't CLIA waived can be lower. So I think you want to be specific.

DR. CALIENDO: Angie Caliendo.

But is it the case that if I looked in the package inserts of the FDA-cleared NAATs, that the lower limit of the 95% confidence level is above 90% or very darn close to it?

DR. SCHERF: Yeah, this is Uwe Scherf.

You're right. And I think, also, one additional note to make to your questions: We

already now established some of these chlamydia and gonorrhea tests with very high performance, yeah, and from our perspective, we will not have the opportunity to now suddenly say they are not needed to be accomplished anymore, unless this Panel suggests for the application of over the counter there are benefits that outweigh the risks, that we should do that.

DR. CALIENDO: That's helpful. Thank you.

DR. MARTENS: Mark Martens.

You're moving this forward nicely, because that was Question No. 3, the minimum performance criteria. So going to 4, I'll agree with Barbara, but I want to say that Question No. 4 says how do you make sure the intended use population is included? And I know Charlotte and I have done many of these studies before, and when we want to get great positive predictive value and sensitivity and specificity, we go to New Orleans, and we get a sexually transmitted disease clinic, and their rate is 30, 40, 50%, and the results come out good. The intended use is going to be for different -- for group A strep, it's going to be pediatrics. For respiratory, it's going to be elderly. For STDs, it's going to be a mixture, you know, of young people. So I think we need to make sure that the intended population is the one tested to get the performance standards that Barbara and I want.

DR. RAND: Ken Rand.

The intended population is generally not one with low prevalence. So it's not really unfair to test a higher "prevalence" population to validate a test, because, you know, these tests aren't made for prevalences of 1 and 2%.

DR. HENRICKSON: Kelly Henrickson.

The prevalence in the elderly isn't that -- I mean the incidence isn't that high, even though the vast majority of side effects and death is. And so, I mean, because with flu it's seasonal obviously. So if someone -- if flu is not here in November or December, like it isn't

most years but can be, and a 65-year-old takes this test, you know, and the specificity is 95%, they're going to have a false positive.

DR. RAND: Well, just because of the seasonality and the fact that there are low and high prevalence periods, I don't think, you know, it means you shouldn't do the over-the-counter initiative or do it, yeah. There will have to be some kind of educational efforts on the issue of prevalence, which is another good reason to link it to the healthcare system, the results of those kinds of tests. And maybe you don't want that for STDs, but maybe you do for the respiratories.

DR. NOLTE: Rick Nolte again.

So with respect to influenza, since it does tend to be seasonal, and many of us restrict the use of the current point-of-care tests to when we've established influenza is in the community, lab, or point-of-care testing, would it be even feasible to think about limiting the sale of an over-the-counter test to the appropriate time? I mean --

(Laughter.)

(Off microphone comment.)

DR. NOLTE: It's like Christmas decorations.

DR. HAMMERSCHLAG: Christmas or fertilizer in summer.

DR. GITTERMAN: Are you proposing to take it off the shelves in July?

DR. NOLTE: Huh?

DR. GITTERMAN: I'm not quite sure what -- are you suggesting some new mechanism behind the counter or --

DR. NOLTE: How do you do it? I don't know.

DR. RAND: Ken Rand.

DR. HAMMERSCHLAG: Retail does it all the time, does that. Retail is always doing seasonal.

DR. RAND: Well, I mean, there's another issue here -- Ken Rand -- and that is, what is the shelf life of the product?

DR. HAMMERSCHLAG: Yeah.

DR. RAND: So it's going to be hard to pull product that has a shelf life of 6 months off the shelves just because it's June.

DR. HENRICKSON: Kelly Henrickson.

DR. RAND: I don't know the answer.

DR. HENRICKSON: The way the State of Wisconsin does it right now is they put out a weekly newsletter, and it says the positive predictive value of rapid influenza diagnostics is very low right now, and just keeps reminding, you know, the clinicians of that constantly.

DR. GITTERMAN: Yeah. This is Steve again.

I suspect, though, the OTC population will not be reading the Wisconsin weekly newsletter.

(Laughter.)

DR. GITTERMAN: I think you have to assume, to some extent, that over the counter will be over the counter, that people will buy it at a 7-Eleven or whatever mechanism, and they have to make it available. There are some interesting things you're proposing, yet I think we don't have regulations to enforce it. So it would be interesting. I mean, I don't want to speculate because it's still something -- but if you're thinking over the counter, you're thinking that you're trying to increase the availability, and sometimes if you restrict it in some ways, you might be defeating your own purpose.

DR. RAND: I've just got another problem, too, is that this seasonality isn't always the same in every -- I mean it's rolling, it's rolling.

DR. HENRICKSON: And geographically, too.

DR. RAND: Yeah, that's what I'm trying to say.

DR. HENRICKSON: Kelly Henrickson.

And so what you're going to have, even if everything was perfect with this, you would have people hearing about the flu epidemic on a cruise ship in the summer and then a whole bunch will be testing. You would hear about a South America flu epidemic, and then people in North America would start testing, and because flu is around all of our planet and being reported by -- and so it would take a lot of -- everyone would have to become, you know, a respiratory virologist.

DR. GITTERMAN: You know, again, I don't mean --

DR. CALIENDO: Go ahead, Kim.

DR. HANSON: Kim Hanson.

I've always thought it's an interesting question about not testing when you don't know that flu is in your community, but then how do you ever find out that flu is in the community?

(Laughter.)

DR. HANSON: So it seems like a great opportunity, actually, where people with symptoms test, and then if you're positive, the educational materials direct you to your physician, and then you might actually want to confirm those shoulders of the season's positive rapid results. And I also think it's a great opportunity to link into other apps that could automatically, you know, tell you or your clinician your positive and negative predictive value based on your community and what's circulating based on FluNet or Google Flu or other, you know, electronic surveillance materials. So I think it really opens up a wide area for better surveillance, in a way, if people follow up with their clinician based on a positive result.

DR. HENRICKSON: Kelly Henrickson.

If they're going to do an at-home flu test, that probably would decrease their

following up with their clinician for most mild influenza, which is the majority of influenza.

DR. HANSON: Right, but I think -- Kim Hanson again -- one of the interesting things was there is opportunity for self-reporting, even if it's anonymous, that I've had a positive test, and could that be tracked at some level, and certainly educating folks at higher risk that need to be tested, to follow up with their clinician.

DR. HENRICKSON: Kelly Henrickson.

I'm all over it as a research tool or as epidemiology. I love understanding respiratory viral epidemiology, and I think you're right; there's a huge opportunity to learn a lot about respiratory viruses, if we can sort out what's true and what's not. But I'm trying to think of how it's going to help that patient and also the general public, because again, I'm not convinced that -- unlike strep or even the sexually transmitted diseases, with flu I'm not sure that treating mild flu with a $50 prescription is really in the public health's interest or in the individual's interest. So that's the problem is that if we're going to have millions of people who we aren't -- we don't really feel we should treat them with antiviral, then I have to look at, well, what are the benefits, what are the other benefits?

DR. CALIENDO: Angie Caliendo.

But Kelly, we're there now. We do these tests, and we probably treat people that would do fine if we didn't treat them. So I think we're confusing two things, and we're also at a place where results from flu tests are being reported up to a cloud anonymously and geographically. And if people chose to do that, that would -- it could actually enhance surveillance. But what you're describing is not an issue around an over-the-counter test. What you're describing is an issue of when do you treat flu and when do you not treat flu? So if someone calls the office and says, Angie, I did an over-the-counter test and I'm positive, and I'm like, how long have you had symptoms, how do you feel, and you talk them through it, I may choose not to treat them, and that could be true regardless of the

test that we use.

DR. HENRICKSON: Sure, Angie, but until you have an over-the-counter test, you won't have the situation where a parent can say, oh, you've got flu, I'm not going to call because you've got flu. They don't call.

DR. CALIENDO: Unless they want the patient treated. Unless they want the kid treated.

DR. HENRICKSON: Right, but why did they just spend -- I mean, is there a benefit? I mean, so then we have to go through all of the positives and negatives that we've already talked about, false positives, false negatives, true positives. I mean, we have to say is there -- I mean, why are we providing this test? Okay, is there truly a benefit to that patient, if it's accurate? Whether they get in contact with the health system or not, is there a benefit to knowing that they had flu? Okay, will they really stay home? I don't think so. Will they really not go to school? I don't think so. Okay. I mean, we keep our resident doctors, who understand it completely, from going and working in the children's hospital with respiratory viral infections.

DR. CALIENDO: Is your comment directly related?

DR. GAYDOS: Um-hum.

DR. CALIENDO: Okay.

DR. GAYDOS: Charlotte Gaydos.

I think there is some benefit to the individual that has the flu and to the family in that if a parent can diagnose influenza in a child, then interact with the doctor to say do I need to treat or not to treat, that clinician can make that decision. But one of the advantages of having that over-the-counter test for influenza is not having to have the mother drag that patient in to the pediatrician or to the emergency department, where people are gathering and spreading the infection, to say does my kid have a strep throat or

do they have influenza? Do they need penicillin, ampicillin, or do they -- if they're sick enough, do they need Tamiflu? So I think that one of the huge benefits about keeping people out of the hospital is to be able to control epidemics, just like for --

DR. HENRICKSON: Kelly Henrickson.

I agree with you, except that the moms and dads are still going to be sending their children to daycare, which is where flu is really going to be. And in school.

DR. GAYDOS: But if that clinician says keep your --

DR. HENRICKSON: Unless they're moderately ill, they're really still going to be sending them. Even if they have flu positive, I can guarantee you that the majority of times the parents are not going to say I'm going to stay home from work because I did this rapid flu test. You look fine. Here's some ibuprofen. Okay. And again, I think we shouldn't lose track of the fact that, except for about 10 weeks of the year, the positive predictive value of the current tests, even with great sensitivity, even if we push the specificity up a little bit, it's still going to be bad. Okay. So for 42 weeks of the year, these tests that we can't pull off the market are going to be useless in really saying that they have flu.

DR. GAYDOS: Then they shouldn't be sold during that period of time. But yeah, I do think interacting to keep people out of an area where transmission occurs, and I do think if they interact with their clinician, then it's the clinician's job to say you need to keep that child home, but --

DR. CALIENDO: So Angie Caliendo.

So Kelly, I think what you just said is very important. I think that comment you made is something we all need to think about, if any flu test is really only useful 10 weeks out of the year. I think, for me, that's very helpful.

Cathy, you have a comment, and then I think we're going to take a break after your comment.

DR. PETTI: This question is both to the Panel and also to the FDA. It sounds like a lot of our public health benefits for these tests rests on the fact that we would like to inform the public, and then truly, then when they have their interaction with their healthcare provider, it is that shared decision making because that individual is informed. And how can you have shared decision making without first being informed? And the availability of over-the-counter tests might be the first interaction where we can start informing the public.

With that being said, is this -- are there areas of gray that we need to explore where -- do we simply want to focus on a one-and-done test, where it's the diagnostic test and it's only going to be done once, and then the healthcare provider needs to trust that since it's an FDA-cleared test? Or do we want to explore a construct before we get the perfect test, of having a confirmatory test, which were some of my comments early on, before we have the molecular test in the hands of the public? So is there a value in providing a test? Our home HIV test, 1 out of 12 are false negative, I think. Is that somewhere around there? Just something to discuss before we say it absolutely has to be this level of sensitivity and specificity. I don't necessarily rest on one side or the other on this.

DR. MARTENS: Mark Martens.

Just to answer you and answer Kelly -- you know what? It gave me another idea. You know, you're right, the woman is going to want to go to work, and she wants to drop her kids off at daycare. You know, the daycare say -- sign them when they come in, you know, when they sign their contract. You know, if your kid has symptoms, we're going to test him, and if we test him, he's got to go home or she's got to go home.

(Laughter.)

DR. MARTENS: And I do that at Wal-Mart and everywhere else, I do it in my office; otherwise -- so that's another use for the test.

(Off microphone comment.)

DR. HENRICKSON: That is a great idea.

DR. MARTENS: Well, that's a way. You're worried about preventing epidemics. That's where they happen.

DR. CALIENDO: Okay, let's get back to Cathy's question. What does the group think about that?

DR. BEAVIS: I just have a specific comment to what you were saying about the HIV testing, and I think you said 1 out of 12 is a false positive. That's better than the hospital-based testing that we do for opt-out testing. Okay, there are two issues. And for me, I'm more familiar with the false positive issues when we do opt-out testing, but it's just sort of the price that we pay when we want to screen all women who present in labor and we don't know their HIV status. And yeah, we've had a couple cases where we do unnecessary C-sections, but again it's part of the big picture, and for each individual case, risk management, the pediatricians go crazy, why are we doing this? But it brings us back to, again, the big picture and all of the patients. Well, you know that none of them are going to be all right or, you know, all positive or all negative in the right populations.

DR. PORTIS: When you say that, part of what I think about is the other issue that got touched on, which was about overtreatment, which we've seen in breast cancer and prostate cancer. And it goes back to Kelly's comment before, that we need the studies to be designed in a way that we can look at the overall public health benefit. And it's true that some people will get caught on either side, but we need the data to understand if these tests do have the impact overall that we want.

DR. CALIENDO: Okay, I'm noting a pause in the action. We're going to take a 15-minute break, and then we're going to return. So everybody do calisthenics and come back with your A game because we're going to go through these questions. And I'll remind the Panel members, please do not discuss the meeting topic during the break amongst

yourselves or with any member of the audience, and we will resume at 3:30.

Thank you.

(Off the record at 3:11 p.m.)

(On the record at 3:30 p.m.)

DR. CALIENDO: Okay, so we're now going to address the FDA questions, and what we're going to do is Dr. Conenello is going to read each question, and then we're going to go around, and everybody is going to comment on each question. And for the first question, the first person will speak, the second person speaks. If it gets to you and you have nothing to add, "nothing to add" is a perfectly acceptable response. Okay, we don't need to go over and over and over. We've been doing that for several hours. What we want is our thoughts and opinions on things. We're going to break it down so that I'm going to start with Mark on the first question, and he's going to respond for flu, and then he's going to comment on group A strep, and then he's going to comment on GC/chlamydia. Then it's going to go to Lizzie, and then it's going to go Kelly, and we'll go around that way.

So first question, please.

DR. CONENELLO: With the benefits and risks described for the over-the-counter testing of each of the pathogens -- and are there any other benefits or risks that should be considered?

DR. MARTENS: All right. I agree with the benefits and risks discussed. As I mentioned earlier, I think we -- I would separate out influenza, group A strep, and chlamydia/gonorrhea. I think the major benefits that may not have been expounded as much I'd liked earlier, with influenza/group A strep, as we saw in earlier data, there is a tremendous over-prescription of antibiotics, probably -- maybe inappropriate antibiotics. And I think that as a director for 153 OB/GYNs, 60 offices in which we have pediatricians in those offices, the biggest complaint I get is now, with patient satisfaction, if a mom calls me

up and says she wants antibiotics for her kid, do I have to give it? So it would be very helpful if we could say no, your home test or your test was negative, and you can come in if you'd like, but we're not going to prescribe you antibiotics over the phone. So I think avoiding antibiotics are a tremendous benefit.

For the chlamydia and gonorrhea, as a gynecologist, I think just the bad outcomes of ectopic pregnancies and infertility and PID are significant, and any test that brings me more patients in, even if they're only half -- half are true positives, is a benefit. So I think we've -- I think the benefits outweigh the risks, and I think they've been discussed.

DR. CALIENDO: Lizzie.

DR. HARRELL: Yes, I agree that the benefits outweigh the risk, and I also think that with the chlamydia/GC, we will probably reach a group that we are not reaching now.

DR. HENRICKSON: Do you want me to say my name? Kelly Henrickson.

I agree with the benefits and risks that have been described in the previous discussions and in the paperwork that we have. I do not believe that the risks outweigh the benefits for over-the-counter influenza testing, but I do believe that they do for group A strep and for chlamydia/GC.

DR. CONENELLO: Benefits don't outweigh the risks or the risks don't outweigh the benefits? Sorry.

DR. HENRICKSON: I believe that the risks and the unknown, because we don't have data yet, are greater than the potential benefits from over-the-counter influenza tests.

DR. RAND: Excuse me, can we clarify what we're talking about here? Are we answering the question on the board or -- which is are the risks and the benefits -- have been presented, is what that says, as opposed to do we think the risks or the benefits outweigh each other? They're two questions. Which one are we answering?

DR. HENRICKSON: And I was following the lead. I'm sorry.

DR. CONENELLO: Yeah. So we've got a little bit of an issue with the questions that are posted up. We'd really like to focus on the way the questions are written in the packet.

DR. CALIENDO: Okay, so let me read the question as --

DR. CONENELLO: Oh, sorry.

DR. CALIENDO: Let me read the question. Do the benefits outweigh the risks for recommending FDA consideration of over-the-counter diagnostic assays for detection of each of the following pathogens:

- influenza;
- group A strep; and
- GC and chlamydia?

DR. CALIENDO: So if I understand correctly, Mark said yes on all three; Lizzie said yes on all three; and Kelly says yes on two, but not flu.

DR. HENRICKSON: Correct.

DR. CALIENDO: Okay, Rick. Question No. 1 in your handout.

DR. NOLTE: In my handout? Okay.

DR. CALIENDO: In today's agenda.

DR. NOLTE: Okay.

(Off microphone comments.)

DR. CALIENDO: What we got today, guys. Go to the last page. Everybody got it? Sorry about that.

DR. NOLTE: Rick Nolte.

I think, for influenza, I don't see the real value in an over-the-counter test. I'm sort of on the fence when it comes to group A strep; I'm not sure whether -- what the risk-benefit analysis really looks like. I am on board with the CT/NG. And I'd also like to add that the original question talked about agreeing with the benefits and risks described in the

Executive Summary, and I think you did a wonderful job in describing those, but those are all potential risk and benefits, and there is very little evidence that's driving any of this in terms of the value here for over-the-counter tests.

DR. HAMMERSCHLAG: Well, I think I'm more confused than I was -- oh, Mark, sorry. See, I'm so confused, I don't know who I am. Okay, Maggie Hammerschlag from New York.

(Laughter.)

DR. HAMMERSCHLAG: I think this has left me more confused. I can see arguments on both sides. As a pediatrician who actually does see patients occasionally and has to deal with it, I'm having a lot of trouble with all of these, quite honestly, being over-the-counter because of the absence of a definite linkage to therapy and the other, you know, potential problems that can come with it, plus definitely for the chlamydia and gonorrhea, we do not have the -- well, I think in maybe 2 to 3 years we will have the technology, but it's a question of how we can link it.

As for group A strep, I think the major problem is going to be collection. I just don't think, with the currently available antigen tests, that however you do it, most of this will be done in children, that they'll be able to get an adequate specimen. If you had a NAAT maybe and a different, less-invasive specimen -- throat culture's fairly invasive -- it might work. Influenza, I guess it really doesn't matter, but I do agree that I think it would be of very limited value clinically.

MR. WOLFF: Peter Wolff.

I believe the benefits outweigh the risks for influenza, for group A strep, and for chlamydia and gonorrhea.

DR. PETTI: Cathy Petti.

I agree.

DR. BEAVIS: Kathleen Beavis.

I agree that the benefits outweigh the risks for influenza, group A *Streptococcus*, and CT/NG.

DR. RAND: Ken Rand.

I think the benefits outweigh the risks for group A strep and CT/NG but not for influenza.

DR. BEANAN: Maureen Beanan.

I agree that the benefits outweigh the risks for all three pathogens.

DR. GAYDOS: Charlotte Gaydos.

I agree that the benefits outweigh the risks for influenza, group A strep, and CT/NG, and that especially with the group A strep and influenza, we could mitigate some of those risks with collection and education by a co-taker of the sample: the mother, the wife, the husband, the partner, whatever.

DR. VAN DER POL: Barbara Van Der Pol.

I'm undecided on the influenza. I think there is a lot of gray area there. I do think that the benefits outweigh the risks for group A strep and for CT/GC.

DR. HANSON: Kim Hanson.

I think the benefits outweigh the risks for all three organisms.

DR. DODD: Lori Dodd.

I think the benefits may outweigh the risks for CT/NG. I'm really undecided about influenza and group A strep because I think it depends entirely on what the diagnostic accuracy is and what the potential prevalence is, as we've discussed. The positive predictive value and negative predictive value are going to depend heavily on this, and I think the labeling and education will be critical.

MR. SIMON: Tom Simon.

I agree with the benefits outweigh the risks in influenza, group A, and CT/NG.

Additionally, the benefits, I believe, for the underprivileged, undereducated, underserved would be there's less time involved, less money, less travel, more convenient, and possibly a better quality of life.

DR. PORTIS: Natalie Compagni Portis.

And I agree with Tom's comments about the benefits for underserved populations. I don't feel that the benefits outweigh the risks for influenza; I do with group A and CT/NG, though I really want to stress the importance of the risk of not getting the public health data that we need with these tests and that we need to be really mindful of that.

MR. KIMES: David Kimes.

I do not see the benefit for influenza, but I do for group A and CT/NG, as long as the sampling elements of it are addressed.

DR. CALIENDO: So, Dr. Gitterman, my assessment of the people's comments is that there is nearly unanimous support for GC and chlamydia; group A strep, strong support but not unanimous; and much more question about influenza. I think the group is going to have comments about ways to mitigate risks for all three of these options. Is there more information that you need to know about this question?

DR. GITTERMAN: No, but we will -- I hope the group -- this is an opportunity simply to discuss something which was brought up before but not amplified on, which is the risk of laryngospasm and collecting a group A strep sample.

DR. CALIENDO: Yeah, I think we'll get to that when we get to mitigating risk, since that's one of the risks of specimen collection.

DR. BEAVIS: And can I just second a risk that Dr. Hammerschlag mentioned earlier, which is a positive CT/NG result in a person less than -- I won't specify an age, but just because of the ramifications of abuse.

DR. CALIENDO: Noted, thank you.

Okay, let's move on to the second question. Do you want to read what we're reading?

DR. CONENELLO: Yes.

DR. CALIENDO: Great.

DR. CONENELLO: Okay, this is the second question. For influenza, group A strep, or CT/NG diagnostic assays that the Panel believes should be considered for over-the-counter use, please discuss recommendations for minimum levels of performance that should be met for clearance.

Now, this can either be a number, or you can tag that to current practice.

DR. CALIENDO: And just for completeness, even though the group's feeling about all three pathogens are not the same, feel free to comment on all three pathogens because I think the more information we give the FDA, the more helpful it will be for them.

Start on this end.

MR. KIMES: All right, David Kimes.

As I stated earlier, it's probably difficult to put a value on it, but at the end of the day, it needs to be as absolutely high as possible for sensitivity and specificity, as well as the positive predictive value and negative predictive value.

DR. PORTIS: Natalie Compagni Portis.

And I agree with that.

MR. SIMON: Tom Simon.

I agree.

DR. DODD: Lori Dodd.

I think it's going to depend entirely on the different, the three different diseases and -- you know, because really what's important is the positive predictive value and, to a certain extent, the negative predictive value. So I did some calculations, and with

sensitivity and specificity of 90%, which would be considered low, I think, in this context, with the prevalence of 10%, the positive predictive value is 50%; with a 5% prevalence, the positive predictive value is 32%, so that's quite low. If you bump that up to 99% in contrast in terms of sensitivity and specificity, the difference between the 10% prevalence and a 5% prevalence goes from 92% for a positive predictive value to an 84% positive predictive value, so that's a big gain.

So I think we have to be in the region of high sensitivity and specificity, but I could see in some context where you're trying to get patients and that you could sacrifice on that a bit, but perhaps for influenza and strep A you might really insist on very high sensitivity and specificity.

DR. HANSON: Kim Hanson.

I agree with what's been said, and as a benchmark, I would consider potentially for flu and group A strep having sensitivity and specificity that's equivalent to the current approved point-of-care tests that are molecular based, and for CT/NG, ideally, on par with laboratory-approved tests.

DR. VAN DER POL: Barbara Van Der Pol.

I do agree that I think substantial equivalence is where we should go, I think, probably with all of these. I mean, they can be better than what we had access to, but I don't think we should go backwards. The only thing I'll say about when we look at positive predictive values, the only figure there that really matters is the specificity, and so it doesn't have to hit a 99/99; it can hit a 90% sensitivity but 99% specificity, and that will keep your positive predictive values up. But there are some things where negative predictive value is more important, so it's going to depend on the analyte, and it's going to depend on the intended use.

DR. GAYDOS: Charlotte Gaydos.

I think that the sensitivity and specificity should be as high as what we currently accept for NAAT tests, 90% sensitivity and 98, 99% specificity. I think it's difficult to make any judgment about the positive and the negative predictive values because they depend on the prevalence in the population, and they will fluctuate as to if you're in a high-prevalence population, they'll be greater; if you're in a low-prevalence population, they will be less.

DR. BEANAN: Maureen Beanan.

I also agree with the sensitivity and specificity being at the levels currently achieved for FDA-cleared products, and I have no real comments on PPV and NPV yet.

DR. RAND: Ken Rand.

I think, at a minimum, the analytic sensitivity and specificity has to be as high as reasonable or high as possible, which basically, in effect, means as high as current nucleic acid tests in use in labs today. Obviously, you know, the predictive value is going to be a function of the prevalence. But I think, you know, having -- building in contact with the healthcare system can help mitigate the risks of low prevalence.

DR. BEAVIS: Kathleen Beavis.

I think that the sensitivity and specificity should be essentially equivalent to the NAAT-based tests that are available today.

DR. PETTI: Cathy Petti.

If the assumption is the intended use and labeling will be for diagnostic purposes without the requirement for confirmatory testing, then I agree with Dr. Hanson's comments and Dr. Beavis.

MR. WOLFF: Peter Wolff.

I have nothing to add.

DR. HAMMERSCHLAG: I agree with what Drs. Dodd, Van Der Pol, and Gaydos said.

Oh, Maggie Hammerschlag. I keep on forgetting that. I think that we want to try to achieve the best sensitivity and specificity that we can, and certainly, definitely for the chlamydia and gonorrhea, because we've got good benchmarks at this point. So I will defer to them.

DR. NOLTE: Rick Nolte.

Nothing to add.

DR. HENRICKSON: Kelly Henrickson.

I agree with the previous comments about being at least at the CLIA-waived level.

DR. HARRELL: Lizzie Harrell.

I agree with what's been said already.

DR. MARTENS: Mark Martens.

I agree. I'm going to answer Question 4 at the same time. If we're going to decide on the sensitivity and specificity, we need to do the testing in an intended population. As Charlotte's test study was before, your rate was 11%. If we go to an STD clinic with a 30%, we're not going to get the results we want and we'll get the -- we'll meet the minimum targets, but we won't get the results we want.

Thank you.

DR. CALIENDO: Okay. Thank you, everybody.

So, Dr. Gitterman, the group all agrees that they want to see testing as -- the sensitivity and specificity as high as possible, and the general consensus of the group was that this should be for GC and chlamydia at the level of our current NAAT tests that are used in laboratories, and for group A strep and influenza, NAAT also, but someone mentioned group A strep, using what's over the counter now, having it equivalent to that, which would be an antigen test, not necessarily NAAT. Did I miss something on that?

(No response.)

DR. CALIENDO: So flu and GC/chlamydia would be what we're doing in the lab, but

group A strep could go to the level of an antigen test.

DR. HENRICKSON: That was 95% correct for CLIA waived. Minimum.

DR. GITTERMAN: Yes.

DR. CALIENDO: Yes.

DR. GITTERMAN: Well, these are two different things. A CLIA waiver, there's no OTC group A strep test now, so the antigen tests don't have to meet the CLIA waiver standard. There are antigen tests out there that, in fact, have lower performance than 95%, so -- well, actually let me clarify that because I'm speaking -- there are antigen tests that do have a little performance historically, but we will come close to it. But the point is you don't have to approximate the NAAT tests, which do better and which we currently don't require confirmatory tests for. The meaning is clear. My historical background is not that good. Can I just make two quick points, if it's possible?

DR. CALIENDO: Yes, but Rick, why don't you comment first and then you can --

DR. NOLTE: Just a clarification on the strep thing, right? We have nucleic acid -- waived nucleic acid amplification tests for group A strep. So I would be in support of having the over-the-counter test show substantial equivalence to that rather than the point-of-care and a waived antigen detection test --

DR. CALIENDO: Okay.

DR. NOLTE: -- for group A strep.

DR. CALIENDO: So, Steve, what Rick is saying is that given that we have waived point-of-care molecular, that that would be the bar that they're -- that people are talking about. My question to you is, is that the same bar for antigen and for molecular?

DR. GITTERMAN: Well, the difference there is that it's a long involved question in terms of what the bar is, because the bar for the 510(k) paradigm can be variable, but the NAAT tests generally perform at the level that Dr. Henrickson is describing. So again, I think

the message is clear, you want it as good as you can, and I don't think we have to argue in this case particularly about the number.

But I did want to make two points where it is important: The first is, just very quickly, there's a little bit of mixing of lower bound of the confidence interval and point estimate. We have both parameters. One is the point estimate, and two, the lower bound of the confidence interval, and of course, sample size is dependent on both of them. So when people are talking about 90%, sometimes I think they mean the lower bound of the confidence interval versus 95%. I have to say our estimates are usually far more precise around specificity because no matter what you're talking about, it's much easier for -- you know, to get negative specimens and test people negatively than it is positively.

I did want to make a comment -- and I apologize, I wasn't certain who mentioned it -- but one of the points about OTC testing is you can't mandate a confirmatory test. We can't say you bought it, now you have to buy something else. I think that might be a little -- you know, that might be a little overreach of the government for that point. So one of the points of it is, which is why the response to this question was so valuable, is that it indirectly addresses the fact that you cannot have confirmatory tests in this setting. So really it was very loud and clear. We can fill in the details.

DR. CALIENDO: Okay, any other comments by the Panel?

(No response.)

DR. CALIENDO: All right, so that's Question 2. Question 3, please.

DR. CONENELLO: Question 3: Please discuss potential risk mitigation strategies that should be considered for each analyte.

DR. CALIENDO: Okay, so this is going to be a little bit more detailed, complicated probably. So when you speak, please speak about each analyte separately so that I can get a general thought and consensus as I go around the table. Thanks.

(Pause.)

DR. CALIENDO: Sorry. Mark, are you going to start?

DR. MARTENS: Mark Martens.

I would see for the -- I think we discussed most of them, but I would see for NG/CT, I would like to have a statement, and if possible, included that states that a positive test puts you at higher risk for other infections which are not included in this test; please see a healthcare provider for treatment or for follow-up after treatment. So I'm very concerned of people thinking they have one disease when they really have two. I'd hate to miss a shallow non-tender ulcer because the patient had chlamydia and I treated her over the phone, and 3 months later, 4 months later when I saw her it was done, and I don't know what she really had. She had syphilis until she develops a rash.

For group A strep, you know, I just think that for both group A strep and influenza, it's mainly the testing and getting the right sample. And we discussed various methods, videos, special testing, I think, for group A strep having a parent or some other person get that. I also like the idea of having another test looking for white blood cells or other proper -- again, I think other people have similar ideas, but I think for group A strep and influenza, that the main issue is getting the proper sample.

DR. HARRELL: Lizzie Harrell.

I agree with what Mark has said about CT/NG. For group A strep, I think, as we already said, the collection is a big concern. And I think for influenza, we also need to put something in the package insert that reminds people that it's a seasonable disease. So if you are in the middle of -- when it's not flu season and you are testing, you may get a false positive, and you should be testing only when there's a high -- when the flu rate is high in your area.

DR. HENRICKSON: Kelly Henrickson.

I agree with what's been said already about group A strep and CT/NG. For influenza, I think that for risk mitigation we have to have, again, as we mentioned, high sensitivity and specificity. But I think the special controls are very important, as they have listed already, which includes yearly testing of current isolates every year and analytical minimums, because there's such broad analytical sensitivity amongst the current point-of-care influenza tests that I think there has to be analytical minimum sensitivities. Specificity is usually not an issue. And analytically. And that includes testing -- the special controls have to include some kind of synthetic nasal material or take into account the variability of the fact that we have demonstrated, through BARDA, that there is just a wide array of inhibitors in people's noses, and so you can't just test a group of children or a group of adults.

You may have a low amount of the NP IgG that is the inhibitory substance that we've isolated and determined. And so it's just a wide variation in human people. So we have started describing that, and there's been some other work on that by others, so we have to have -- the FDA has to agree on what kind of material the analytical testing is going to be done in so that it actually demonstrates true sensitivity.

DR. CONENELLO: Can I ask a clarifying question? Do you think that pooled samples are appropriate, or do you think it needs to be individual --

DR. HENRICKSON: No, individual and pooled don't work. That's what we just got done spending 6 years of BARDA's money looking at, and it's -- there's just a wide variety of inhibitory substances because all these are based on NP antibody interactions. Now, obviously, if the technology is different, nucleic acid amplification is not inhibited by any of this, and so it really doesn't matter. We found that you don't need the synthetic kinds of nasal secretions. But you really have to put it in an average amount, so you have to find an average of that, and you won't know for sure if you just take 10 people and mix it together and pool it. That's what we've done before. I've spent 26 years doing this, and that was the

standard: you just pool it. But for an antigen-based assay -- it works fine for nucleic acid; it does not work for antigen-based assays. And we have a publication that's in -- that's pending right now on that. So I think you have to have special controls, and you guys, I think, understand that and that's -- you had listed some of these things in your handout. I think I agree that for mitigation you have to have user studies, important user studies, and things that I've been assured we probably can't do a lot of other mitigation things. So I'll stop there.

DR. NOLTE: Rick Nolte.

I think I agree with most of what's been said. I just want to follow up on Mark's issue about the risk of someone who tests positive for a CT or NG is probably at risk for other sexually transmitted diseases. But also, if they buy the test and they test negative, aren't they -- I mean, aren't they concerned about exposure and that there may be -- I mean, there's a tricky issue there, too, about the simple fact that they tested themselves for CT/NG means that they might be at risk for others, so it's not only the positives, but it's the negatives.

DR. MARTENS: Right, they may have Trich, and they say I don't have anything because that's testing back negative. No, I understand.

DR. NOLTE: Yeah, so that education piece of it.

DR. HENRICKSON: It should say if you're doing this test, you should test for all the sexually transmitted diseases, and by the way, are you pregnant?

DR. NOLTE: Yeah.

(Laughter.)

DR. CONENELLO: Can I offer a suggestion, perhaps something along the lines of if you have engaged in any of these following risky behaviors --

DR. NOLTE: Risky, exactly.

DR. CONENELLO: -- you should seek further testing --

DR. NOLTE: Um-hum.

DR. CONENELLO: -- regardless of the results, something like that?

DR. NOLTE: Yeah.

DR. CONENELLO: Yeah.

DR. NOLTE: Yeah. Yeah, I think that -- yeah, that's all I have.

DR. HAMMERSCHLAG: Maggie Hammerschlag.

I concur. I think that's a good way of dealing with the chlamydia and gonorrhea issue. I think that for, again, going back to the group A strep, I think that with the current antigen tests, there may still be a problem with collection. If we were up to a level of a NAAT, then it may be possible to use less invasive specimens, and that's something that, I think, is needed for study.

MR. WOLFF: Peter Wolff.

I have nothing to add for the influenza and the group A strep. However, for the chlamydia and gonorrhea, I think education materials are really important, and the readout needs to be as simple as possible, something along the lines of yes, you have gonorrhea; no, you do not have gonorrhea. Very specific. And then I'd also like to borrow some language from the OraQuick panel recommendations to include language something along the lines of retesting is recommended if you test negative and continue to engage in behavior that puts you at risk.

DR. PETTI: Cathy Petti.

I think we should have some emphasis on our user experience, instructions for use, and how to perform the test, I think the most rigorous requirements and the highest level for all three. Assays are extremely important. I don't know if the FDA sets ranges for acceptability on instruction for use testing, but I recommend that that would be in the

highest percentile.

DR. CONENELLO: Currently, we require that it be at a seventh grade reading level or below.

DR. PETTI: Oh, I'm talking about the success of the user comprehension studies.

DR. CONENELLO: Okay.

DR. PETTI: So first, the instructions for use studies on how to perform the test; then the human factor studies, actually performing the test itself; and then finally, the user comprehension studies when the consumer is being evaluated on how well they comprehend the test. I think all three studies would need to be in a very high success rate. Also, I think from reporting out results, we've learned that consumers see results in different ways, so text is one method. But I think a recommendation would be having three different ways to communicate results, one text, one graphical, and one maybe through pictures, you know, green/red. I know people are challenged by colors. Yeah, oh jeez, yeah, a smiley face or unhappy --

(Off microphone comment.)

DR. PETTI: Yeah. And then finally, I think it's imperative for actually all three to have either online resources and links for consumers to go to after they receive a test result, as well as for perhaps GC and CT, a true hotline to talk to a counselor. And finally, from a consumer safety standpoint, I would like to recommend to the manufacturers that FAQs be included in either the package insert or perhaps on a website such that, as we all know, the same questions will be asked over and over again, and the top 10 could be highly informative to that consumer.

DR. BEAVIS: Kathleen Beavis.

I'm so glad Dr. Petti went before I did because I can say I second and agree with what she said. Two comments -- and again, this is things for package insert or whatever's going

to be with the products. I think for all three, some kind of statement to the effect that this standalone test doesn't replace a full evaluation by a healthcare provider. And for chlamydia/GC in particular, my big risk, you know, or what I worry about at night is a false positive for someone, you know, who gets that result, is in a relationship, it affects them, it affects their partner. And for chlamydia, if we could consider a special bold thing that says false positives occur with this test and, you know, something to this effect: Please contact your healthcare provider for therapy and a discussion of risk factors. But for that one in particular, I'd like to highlight the false positive.

Thank you.

DR. RAND: Ken Rand.

I would certainly agree with the comments that have been made and add one more comment, really relevant, mostly for influenza. One of the risks of having these tests is a viral modification over time, and they can become less detectable by the test. And so if there's not ongoing monitoring of the viral sequences that underlie the test -- and that should be the manufacturer's responsibility, in my view -- I think that -- you know, I think we need to have that in order to mitigate that future risk and then consider the question of whether the risk-benefit on influenza changes, if influenza becomes resistant to neuraminidase inhibitors as the 2009 standard flu did before it was at one level, thankfully, at least at that level, thankfully, replaced by the swine flu that was susceptible.

DR. BEANAN: Maureen Beanan.

I would also like to second agreement with Dr. Petti's remarks. They were excellent. Also Dr. Beavis' remark related to package insert information for interpreting test results. So perhaps for flu, if you get a negative test result and you still have symptoms, I mean, you bought the test because you have symptoms, there may be worth in adding a statement that you may want to consider consulting a healthcare provider for additional testing if your

symptoms persist or get worse. That's all I have to add.

(Off microphone comment.)

DR. BEANAN: Right.

(Off microphone comment.)

DR. BEANAN: Right.

DR. HAMMERSCHLAG: Maggie Hammerschlag.

But also people with multiple viral infections, too, at the same time, and symptom complexes overlap, so that doesn't mean that you don't have a viral infection.

DR. BEANAN: Yeah. That's -- so yeah. Again, if they're sick and they get a negative on the flu, they may want to consult a healthcare professional for additional testing.

DR. GAYDOS: Charlotte Gaydos.

I think Dr. Petti and Dr. Beavis summed it up pretty well that we need to emphasize, take advantage of the education of package inserts, that we need to indicate that these tests are not perfect, that they could have a test that is wrong, and that this would be mitigated by the fact that you have good clear directions for how to perform the test with diagrams, and if necessary, for people who have low reading ability, if they want to go to their smartphone and have a link for an online video.

I think the idea of having a hotline that they could access might be very costly for a company to provide, but -- and that we should make sure that we tell them that even though they're positive or negative, that if they engage in certain high-risk activity such as dot-dot-dot-dot, they could still be -- this is for CT/NG, obviously -- they could still be at risk for other STIs, and that if they have these risk factors, they may want to consider seeking healthcare. I think a caveat for the influenza test is that maybe we should only sell them in and around the flu season and not make them available in June and July, at least in this country. And then I think the idea of frequently asked questions is a great idea because I

think many users would find this is a valuable resource.

DR. VAN DER POL: Barbara Van Der Pol.

Most of what I've got written down has been said. I will say one response and somebody talking about a hotline, ASTDA is always -- they've got resources to do that, they already have people manning it. So I think that that's a resource that exists that we could link in with or people, manufacturers could link in with. I think that kits need to do -- do need -- they are an intervention opportunity from an education perspective, so they need to have multimedia educational content, URLs, YouTube, written documents, pictorial documents, about the test itself, about instructions for performing the test, about your risk factors, understanding your risk factors, and so on.

I do think that one of the lines that should be in there where it says that this test may be wrong sometimes and a negative test doesn't guarantee you don't have infections, there should also be a caveat there saying this is particularly true if you were only exposed last night because, you know, they're worried, well, they go to a party on Saturday and they want to test on Sunday, and that negative result might be really meaningless. And so I think that, in the case of STDs, we do need a little bit of extra special oomph to get people in that right mindset.

I think a suggestion that would make sense to mitigate the risk that was in some of the Executive Summary about using female urine when that's not always ideal would be to ask manufacturers to always use separate packaging by gender so that, you know, a woman's kit is a woman's kit and a man's kit is a man's kit, and so that would help stop women from doing a urine specimen. I think that there should be assay data on some sort of card or something that tells exactly what test was used, gives a little bit of information from the package insert, and that the patient can write down the date and their result, and they can take that with them if they go in and seek care, because then the clinician has an

idea of do they trust this result, right, because you're not going to know -- the patient's never going to remember that I used -- you know, I used Alere versus Quidel versus whatever. I mean, it's just going to go right in over their head, right? So that would be helpful. And finally, if there could be any sort of tool that would make reporting possible, so whether it's an online tool or some other tool where you could mail in your results to your local county health department.

DR. HANSON: Kim Hanson.

I think most of what I had written down, as well, has been said. I will add just two things: In addition, I think looking at changes in influenza viral sequences, that for all three organism groups, manufacturers should really think about how they're going to do postmarketing surveillance, and is there a way to confirm once these tests are in use in the intended populations, that they're performing as we thought they would in the clinical trials? And one more comment about the influenza packaging. I think I would go so far as to specifically list who the high-risk groups are for severe sequelae from influenza and make sure it's clear that those individuals should seek medical care if their test is positive.

DR. DODD: Lori Dodd.

I only have one thing to say in follow-up to the flu comment, and that is I would like to understand if the FDA has plans for special controls to update the labeling real-time, maybe slap a new label on if it's found that the test isn't actually detecting that particular strain that year.

DR. CONENELLO: Yeah. So the current special controls which would apply to rapid influenza diagnostics that are being generated since the up-classification is closer to being finished than it was last year or any of the previous years. And built into that is a system where if a new virus is not detected, that information is made available in the package insert and on the CDC's website where all of the performance of -- analytical performance

of each test will be listed. So that is built in. And as these tests come on the market, because there's no specific over-the-counter regulation that will be included in that regulation, so they will be subject to those special controls.

DR. DODD: So presumably, I'm the consumer and I go in to buy a flu test, and I would see a new label that's been -- somebody's come in from the company or whoever and put a new sticker on that says it's not picking up this year's strain --

DR. CONENELLO: Yeah.

DR. DODD: -- that kind of thing?

DR. CONENELLO: So the testing is required by August, when the regulation goes into effect, so it should be new for every kind of new flu season.

DR. GITTERMAN: Right. Yeah, to address -- you know, just to fundamentally pull this back a little bit, you know, one of the requirements for CLIA-waived testing -- and again, I think, as Dr. Conenello put it, you know, each is a subset, and she's completely right; if we require the viral update and that's analytical testing, so to speak, does it match it? But just taking this back a little bit, the overwhelming, sort of, mantra of over-the-counter tests is simple and easy to use, and the idea that we'd be explaining to people that it captures this year's strains, or a lot of FAQs or a lot of things which I'm not even sure most medical students appreciate, may be adding a lot of complexity.

I guess the general point would be if the device out there does not match the strain so that it's underperforming, in the case of influenza, specifically, because being -- you know, having performance that captures a strain, it would likely be asked to be removed from the market, and in that case, I don't think we'd be putting stickers on it. Now, a manufacturer, for advertising purposes, might say new and improved, you know, gets this year's strains, that's a different issue. But if a test was grossly underperforming, which is the example we talked about before, that it's not performing to specifications or is unlikely

to do so, that might be a requirement. Flu is a little bit different in that regard than the other tests.

DR. DODD: Thank you. That's helpful.

MR. SIMON: Tom Simon.

Dr. Petti mentioned almost everything I was going to say, as well as the people after. But two things, if I didn't hear them correctly -- and one is probably obvious. Appropriate languages have to be -- it has to be in appropriate languages. And one other thing would be a listserv whereby, if it's feasible and possible, that people who are taking the test can take the test or have the disease, they can go online to a listserv and discuss with other people who have taken the test, who are thinking about taking the test, and they can discuss with them anonymously back and forth amongst 10, 20, 1,000. I know a number of listservs that exist where thousands of people are on, and you can get information from everybody.

Thank you.

DR. PORTIS: Natalie Compagni Portis.

I agree with what Dr. Petti and Dr. Beavis said, and I think having information -- and Dr. Martens brought it up, too -- that really stresses the risk, especially with the STIs, to be tested for other things and the importance of that. But then to Dr. Gitterman's comments, part of what I'm concerned about, too, is as we discussed before, there's all this material. How do you get people to read it? And I think we need a lot of consumer input from actual, you know, people who are really going to use this test, to say what did you see, what did you read? You know, the equivalent -- I know it's not the appropriate thing, but like a black box warning, like what's the most -- what do we really want to communicate, because we know that people don't read these pages and pages of information, so I think we've got to find a way to balance that out, and so I want to stress that piece.

MR. KIMES: David Kimes.

I know I had indicated earlier that I didn't see the value with influenza, but if it does go forward, I think there has to be a lot more focus on the high-risk populations. Now, my comments are going to be more from a design perspective. I agree with all the clinical commentary, so I'm going to try not to rehash that. But with influenza, you know, the high-risk populations, especially the aging, if it's not right, the morbidity can change, you know, so I think we really have to be careful there. With the other two, the strep and the CT/NG, I really believe design controls need to be applied. Any discussion around CLIA waiver does not apply here because we're not in a clinical laboratory; we're in a home. So I think, you know, that that's a fallacy, you know, as I listen to that.

Now, the reason I say that is that the human factors component of this is absolutely paramount. It has to be significantly studied. We're basically taking the doctor's office and bringing that into the home, and those techniques, they're not -- even a laboratorian doesn't know those techniques, you know, so -- you know, we have to make sure that, you know, that is the most significant part of the design controls on this because it has to work. We get there with training. We've talked a lot about how to get -- to manage that, and I agree with that. And a comment was made earlier about clinical learning. I never thought of that until I heard it today, but yeah, we have to be very careful in the clinical trials not to set that up, because we have to see how people act first, so we may not be blocking studies like we usually do.

And then finally, Natalie, to your comment, I completely agree. I started thinking about I buy a piece of electronic equipment and I get this manual, and I get this sort of quick reference guide. You know, we need a quick reference guide to capture all of those important things that everybody said so I'm not on page 52 of the guide to find that important statement. You know, just get all that stuff up front.

DR. CONENELLO: Just as a point of interest, CLIA waiver devices do have a quick

reference guide, and I think that's very easy to implement for an over-the-counter. It's usually a short one-page card that now we try to focus on having visuals as well.

DR. NOLTE: That's also true for moderately complex and high complex tests that are done in the lab. We have our own little quick reference guide.

DR. PORTIS: Well --

DR. PETTI: I just wanted to --

DR. PORTIS: I just want to say your point is a good one about presenting the materials in different ways since we know everybody doesn't get the information the same way.

DR. PETTI: And just adding one more point about postmarketing surveillance, I know we all can't predict the sequence variations of virus and bacteria, but equally unpredictable is human behavior with test results. So I would recommend to the FDA to consider a voluntary program for postmarket surveillance for our manufacturers to follow human behavior after receiving these test results, particularly a GC/CT test in more of a perspective of patient safety.

DR. CALIENDO: Okay. So, Dr. Gitterman, I'm going to summarize in two ways: one, what the Panel recommendations or thoughts are that kind of apply to all the tests, and then I'll look at each of the three pathogens and what specifically there were concerns about. So one is having instructions for use that are very simple, a quick reference guide, in a level of education that is appropriate in multiple languages; have the readout of the test be very, very simple, and include the opportunity to not only have pictures, but go online and look at what test results could look like so that it will help guide people. The studies to be done for any of these would include comprehension tests, human factor tests, and results interpretation tests, as was pointed out earlier today by one of the people in public speaking. Online resources in many -- as many formats as we can think about, and you

need to get young people in the room to think about this, not just peri-geriatric folk like kind of on this Panel. I think the utility of a hotline, should we have counselors available? I think that is all -- that probably the counselors probably applies more to GC and chlamydia testing than it would be for group A strep and influenza. There was a lot of positive thought around educational material in the form of frequently asked questions, also using it to educate people about the biology of the infections. The point was brought up that, you know, you can have high-risk sexual behavior today and you're not going to test positive tomorrow. And I think taking advantage of every route we can consider to educate the public and actually clinicians, too. There was a comment made that the standalone test does not replace an evaluation by a provider. I think that's very important.

I'll talk about GC and chlamydia in a minute, but for flu there was just a lot of thought on focusing, too, on the high-risk person. We talked about package inserts, simple readouts. So I really like the -- so let's talk about some of the concerns that the Panel has. Let's start with GC and chlamydia because there were a lot of concerns there. And one really interesting comment that was made was separate packages based on gender, so have a blue package and a pink package; you buy the right one, which gives you a clear description on how to collect a specimen. I really like the idea of filling out -- having the data on a card that they just fill in the results and they bring it to their provider.

I think these are the types of things that can really reduce the risk of not understanding a result or a physician not having any clue what the patient is talking about, so I thought that was really good. I think the concerns about GC and chlamydia really focus on linkage to care. Are you going to get treated? They focus on are you going to be tested for other sexually transmitted infections? I think this is a resounding concern by the group. Are you getting retested when you're supposed to get retesting? Do you understand that this test is not perfect, that, you know, there are false positive results and why they

happen? There are false negative results? I think that we need to, for GC and chlamydia, really focus on ways for public reporting. If you can design something -- it came up earlier today where, I did my test and now I'm going to go to an app and hit yes, I was positive, or I was negative, and dump that into the cloud. You can put a location with it with everything else, no other data with it, and I think it may actually enhance our public health screening. So those are the concerns that were raised about GC and chlamydia.

The concerns that were raised about influenza had to do with the performance of the test. We know how variable the -- how much drift and shift we see with influenza; how is that going to impact and how are we going to know that's being impacted? So testing every year, people were very much in favor of, the same design controls that were put in place for the antigen testing, testing every year, testing new strains. I think something has to be done in the package insert about off-season testing, understanding when the disease actually circulates, who are high-risk patients, so that they understand that they should be tested. Postmarketing surveillance also is very important for influenza, maybe more important than any of the three pathogens that we're talking about.

Something that came up early for group A strep and flu was we have -- all have expressed today concerns about proper specimen collection. Ironically, STIs, this seems to be less of a concern; we've done so much work over the years. But for the respiratory specimen and the group A strep specimen, I think there's still a lot of concern of how are we going to assure that, one, the patient understands how to collect a specimen; is there a way built into the test to assess the quality of the specimen? And I think -- did I forget anything? Does anyone have anything to add to that? Go ahead.

DR. VAN DER POL: When you mentioned the seasonality that needed to be mentioned in the flu insert, that actually should be on the outside of the packaging because the consumer should know not to waste their money buying it. I mean, you'd hate for

somebody to buy one in June and they get it home, and inside it says don't use in June, right, because they wouldn't necessarily know that otherwise.

DR. CALIENDO: Okay.

DR. HENRICKSON: Unfortunately, flu -- Kelly Henrickson. Unfortunately, flu can peak on November 7th or it can do it on March 7th, so it's pretty hard to put that on the package insert because -- I mean, yes, most of the time it's January and February, but every 4 or 5 years, it's, you know, November.

DR. RAND: Ken Rand.

We just had three or four flu-bies in June, even one in July.

DR. VAN DER POL: Okay, they can use it in June.

(Laughter.)

DR. NOLTE: May I ask an appropriate question? Rick Nolte.

If these are going to be -- are they going to be -- I don't know what your rules are. I mean, with drugs, I can't turn on a television show and not hear the side effects of Viagra. If we're selling over-the-counter -- I mean, I haven't seen an ad for an over-the-counter pregnancy test on television, but is that permitted?

UNIDENTIFIED SPEAKER: Yeah.

MR. SIMON: Clearblue Easy, isn't that something -- that came to my mind. Wasn't that a pregnancy test or --

DR. NOLTE: Is it?

(Off microphone comments.)

DR. NOLTE: Okay.

(Off microphone comment.)

DR. NOLTE: You don't get advertising? But I mean, that's part of the --

DR. GITTERMAN: Yeah, they would have to --

UNIDENTIFIED SPEAKER: Pregnancy test ads.

DR. NOLTE: No, but I mean, that would be -- I mean, it's not -- it would be a way of educating, right? I mean, it would be a way because you have to list all the -- like, with the drugs, all the side effects, bad things that could happen, right, that sort of thing?

DR. HAMMERSCHLAG: In very small print, very fast.

DR. NOLTE: Yeah.

DR. GITTERMAN: This is Steve Gitterman.

If they did advertise direct to consumer, which is what you're describing, they would have to -- you know, they would have to reflect the relevant regulations and guidance on balance, etc. So the answer is yes, they would have to fit current FDA guidance and regulation regarding advertising. They couldn't simply say yes, flu comes all times of the year, ignore Dr. Henrickson, or perhaps listen to Dr. Henrickson --

DR. NOLTE: Um-hum.

DR. GITTERMAN: -- and not say, you know, what the balance would be.

DR. NOLTE: Okay.

DR. CALIENDO: So, Dr. Gitterman, any other additional information that you need?

DR. GITTERMAN: No, I just want to clarify a few things that I heard. We certainly did hear the circularity regarding STIs pretty much. If you're buying this test, you should see a physician, but because -- you know, again, as was pointed out, if it's positive, you should see a physician; if it's negative, you should see a physician. But clearly, the Committee, in their earlier responses, had said that the specific characteristics of GC/NG are sufficient to merit testing for those alone in the OTC setting, absent being able to test for the other issues. So there wasn't a concern, again, about having those available in the OTC. I did hear, again, a lot of things expressed. I do have to say I have some skepticism about a voluntary anything because, you know, voluntary means it's out of our scope basically, and it just means, well,

we think it's a good idea, which may not translate into anything after. One thing we have strongly considered and we thought about coming in here, and I'm surprised nobody brought up, is there's a great commonality among all the tests. I mean, the risks/benefits of CT/NG tests are going to be largely the same, and there will be some unique characteristics to individual tests, but they're going to be the same. And again, the bar for that first company is exceptionally, exceptionally high in terms of the materials they would have to develop, the performance.

There is that paradox which we'll have to figure out because, again, we heard you loud and clear, you know, like just even talking about a label that may sort of get around the fact that for an OTC test, the vast majority of people are going to toss it, you know, away, the same way anybody who has a prescription tosses away what they get from CVS or somewhere else, that it has to be simple, safe and effective, and simple and easy to use. And the more provisos we put in there is going to be very difficult, like putting in a test after you bought it and paid for it that maybe you shouldn't be using it. I don't think people are going to say, jeez, I think I'll hold on to this until next fall. I think it's --

UNIDENTIFIED SPEAKER: And then the next line says only good for 4 months.

DR. GITTERMAN: Right, exactly. So there's a real lot to digest, but I do think, since there is a lot of commonality, there's -- perhaps the manufacturers will hear this -- some very expert partners in the room, and a lot of these activities which we're talking about where each company individually decides how they're going to discuss it with physicians or how the public health could be reporting. Again, there's other partners that might have a very vested interest in these things. An enormous amount to digest --

DR. CALIENDO: So I think, Steve, you make an interesting point. There's no reason that the manufacturers could not have common education material. Their tests may be different, but -- and have it online. I mean, you don't have to reinvent the wheel 10 times if

this happens.

Okay, anything else before we go to Question 4?

(No response.)

DR. CALIENDO: Okay, give us Question 4.

DR. CONENELLO: Okay, Question 4, we're going to focus a little bit more on the clinical study design. So please discuss recommendations for ways to ensure that the appropriate intended use populations are enrolled in studies for the clearance of over-the-counter diagnostics for the analytes discussed. Some examples of this would be specifications on recruitment locations, inclusions, specifications about including high- and low-risk populations, and age range requirements.

So I'd like you to be specific for each analyte, what kind of populations you think absolutely have to be included in these, in the clinical studies.

DR. CALIENDO: Dave, you're up.

MR. KIMES: Yeah, it's Dave Kimes.

My comments will be brief because I think the clinicians are the better ones to answer this question, but of course, the demographics are very, very critical. And depending on how that comes together, the labeling may need to contain some type of age limitation depending on, you know, the data that is able to be collected and what that data shows.

DR. PORTIS: Natalie Compagni Portis.

I think that we absolutely need to do outreach in underserved communities and communities of colors and that the outreach can be in schools and churches and salons and other places, you know, community gathering, and for when you're looking at the 15 to 25 demographic, that maybe you'd use social media more, which would be a very different outreach. But I think those are really important.

MR. SIMON: Tom Simon.

Just to add on to Natalie's, the recruitment outreach and obviously the awareness strategies have to go to all the different groups and make sure that you keep it as simple as possible and you get the word out in every way possible. That's general.

DR. DODD: Lori Dodd.

In addition to the population-based testing, which I'm going to let clinicians mention, I guess one question I have is to what extent stress testing needs to be done in this kind of setting, you know, settings that will really challenge the diagnostic performance of these tests?

DR. GITTERMAN: Could you clarify exactly what you mean by stress testing?

DR. DODD: So are there specific populations or specific cases that will be difficult to diagnose with a given test? So it's a little harder for me to -- I'm not an expert in influenza and in strep or in chlamydia, but you know, in some cases there are -- for example cancers, breast cancers, there are certain kinds of cancers that are very difficult to diagnose. So when you're evaluating a new mammography technology, you will find -- you will identify a cohort in which it's very difficult to diagnose that breast cancer and evaluate the sensitivity and specificity in that setting, and I guess my question is to what extent -- does any of that apply here, or is it -- because that tells you when the test may break down, or is it really just an interest in population-based testing and simply identifying the correct population and understanding the interface of the person administering the test and the operating characteristics associated with that?

DR. GITTERMAN: That is such a complex question in so many ways, and it's sort of fundamentally -- it gets into semantics, when you say the intended use population. Now, as the discussion went before, one is when we say biologically stressed populations, to some extent we're just talking about the nature of the disease being different between other

people. That's certainly a question of LoD and analytic characteristics. When you talk about clinical sensitivity, even though I'm using the term wrong, then you're talking about the test as used in the situation. So the fact of once you start introducing errors in every way, shape, and form in collection and running the test, etc., that may lower. Now, to say that enrolling a large population enough so you get all populations, including those who may be stressed, if I'm using the term correctly, by being low literacy -- not to insult people -- by getting populations for whom the test will have the intended use but might be more likely to mis-perform that, we would like to do so.

But that becomes very challenging in a lot of ways, and I suspect, you know, manufacturers or people doing the studies will have a vested interest in enrolling as little as possible because we say there's an absolute requirement that you, you know, match a molecular test to do that. There's a lot of competing risks. And again, there's limits on what a manufacturer can do, and this relates to so many issues. Perhaps we could talk about it afterwards, but to answer it in 25 words or less, there is guidance regarding the nature of the populations. We always have, and it's in every one of our letters, you need to enroll the intended population and get -- you know, it's in our guidance -- ethnic, racial, gender -- although I'm not quite sure that would be true for a vaginal swab -- populations. And again, we try as hard as we can to get the specific intended use population to do that kind of stress testing. But it's difficult, and it's a very challenging test. I could put another -- I won't.

DR. CALIENDO: Okay, Kim.

DR. GITTERMAN: I'll leave it at that.

DR. HANSON: Kim Hanson.

So I don't know how much detail to go into on kind of ways to ensure appropriate intended use populations are enrolled, but I would say for influenza, it will be a large study

because it's going to need to include infants, children, adolescents, adults, and elderly, some that are otherwise healthy and many who have risk factors for severe influenza. So finding them in the community and also through providers' offices as well, I think, will be essential. For group A strep, I would think you'd really want to focus on kind of that 5 to 15 age range and whether or not you could partner with daycares and local schools to identify children to get enrolled in trials. That would certainly require IRB. And also maybe hanging out at pharmacies to tap parents as they come in looking for over-the-counter remedies for flu or for pharyngitis and group A strep.

I'll defer to some of the STI experts here, but I would think for CT/NG, again, focusing on the high-risk populations in that kind of teen and 20-year-olds, teen peer groups, social media was mentioned, college campuses, as ways to identify high-risk patient populations, as well as enrolling folks who do access resources through STD clinics, even though they're folks who are accessing care, but would be at least identifying that high-risk group for intended use.

DR. VAN DER POL: Barbara Van Der Pol.

I'm just going to stick with chlamydia and gonorrhea. Somebody mentioned that they thought that people shouldn't be recruited from STD clinics for these types of trials, but on the one hand, those are the people who are likely to have these diseases, and they belong to the social networks of many of the people we're not reaching, and so while they're not the exact same people, they're very similar. And one of the difficulties with STD testing is for men with urine, we could collect a urine sample and run a number of samples off of it, but for the women, we're going to have to collect multiple samples, and so often, a clinician is going to have to be involved. So this is not going to be something you're going to do at a health fair or you're going to even do at a high school, because high schools and middle schools aren't really that happy to have testing done as a routine thing, much less as

a research activity. So the difficulty with actually getting the research studies done in those populations is fairly overwhelming.

The other problem is you're really looking for the CT/GC. You're hoping a lot of asymptomatic people will use the test; that's what we've been talking about all day. And so while the people coming to an STD clinic may be symptomatic, not all of them are, and so you could still test the asymptomatic ones. The problem is GC. Your sample size is 100% driven by asymptomatic male GC. You're lucky if you can get seven after enrolling -- and I'm not making these numbers up, after enrolling 3,000 people. You know, asymptomatic male GC is just rare as hen's teeth.

So maybe nobody needs to develop a point-of-care test for that. Maybe the point-of-care or over-the-counter test needs to be for chlamydia, and that's fine. But keep in mind that, you know, if we're thinking about where can we get these people, where can we access these people, our STD clinics are still actually a very powerful tool, and we could restrict so we could say maybe 70% of the people in the study have to be asymptomatic rather than, you know, just whatever mix comes in. But I think that it's actually -- that's a very, very big and important question for discussion.

DR. GAYDOS: Charlotte Gaydos.

I agree with everything that has been said. This is a very difficult question, and we want to have wide representation: symptomatic, asymptomatic, wide geographical and racial representation. I agree with Barbie that the STD clinics are probably going to have your prevalence, and you can approach people to be in studies. They're used all the time for studies. They have a high prevalence, and so you'll get positives so that you can measure sensitivity and specificity. I would also mention that family planning clinics are good places, Planned Parenthood, where the prevalence is apt to be lower. This is for chlamydia and gonorrhea. And then high schools, the ones that have school-based clinics,

can be used for research because they usually are separate from the school, funded by either city or county health departments. It's very difficult to do any research study in a school, but they do have prevalences. Colleges, unusually, you would not think, but they really don't have a lot of gonorrhea and chlamydia, when you look at studies that have been done in colleges. You would think that they would, but they really aren't real high prevalent populations.

(Off microphone comment.)

DR. GAYDOS: They're high risk, but they know how to mitigate their risk by the time they get to college. And then could you enroll patients from a pharmacy when they come in, that's something that could be explored, that they could be asked to go home and you know, take home a self-collection kit. But the problem comes is how do you get the comparator test? So that's the issue. So you're almost always linked to somewhere where a clinical sample can be taken by a health professional.

As far as strep and influenza goes, I would think that you could easily do strep in daycare centers and schools. And for influenza, that's a little more difficult whether or not you could do studies in geriatric centers and nursing homes. They do have a lot of disease, but I don't know that they all could give informed consent, so I think influenza is a big problem.

That's all I have.

DR. BEANAN: Maureen Beanan.

So I have a little more out-of-the-box ideas for perhaps chlamydia and gonorrhea, and that would be community outreach to workers who visit with sex workers. I know that there's programs where individuals go out and visit and ask them about their health status and also do HIV testing; try and do that. You could have a testing night at a nightclub, have a healthcare worker go there, set up a sort of booth, and have them do the test early in the

night and see how it works out.

UNIDENTIFIED SPEAKER: But you get all the comparative testing.

DR. BEANAN: Well, there would be the healthcare worker there to take the real, I mean, the actual sample, and then they would do it themselves right there, if they wanted. I mean --

UNIDENTIFIED SPEAKER: Sure.

DR. BEANAN: -- kids are not us. They like to try new things. But anyway, it's just an idea.

UNIDENTIFIED SPEAKER: Health fairs.

DR. BEANAN: Health fairs, sure. For flu, yeah. Nursing homes, maybe not, but maybe retirement communities. Again, you can just set up a station there, and they can come by the community center if they're feeling sick and try it themselves. They might like it. You know, my senior relatives like to try new things. They had smartphones before I did. Shopping centers. So people go out to the grocery store when they're not feeling quite 100%, or drag their children to the mall. And again, it's an opportunity for them to try something new there, and they would do the test there. And again, a healthcare worker would be there to get the appropriate comparator sample. Those are just some of my ideas.

DR. RAND: Ken Rand.

This is really out of my expertise, so I agree with what's been said and what is to be said.

DR. BEAVIS: Wow, you haven't heard me yet.

(Laughter.)

DR. BEAVIS: This is Kathleen Beavis.

No, I agree, there's some nontraditional places where we can do this. And even

though we've been thinking of these are one part, the collection and the testing, there might be some opportunities to see if 14-, 15-, 16-year-olds can actually perform the test independent of whether they're able to collect the specimen at that site. You know, there's special issues working with detainees, but you know, in Cook County jail, we test the women coming in for STDs. That's a great area, when they give their urine sample, to be able to do a self-collected swab and have them practice actually doing the test. You get a good population there. There are issues. Obviously, you want teenagers, not my teenager, but you want other teenagers --

(Laughter.)

DR. BEAVIS: -- able to do this test. But they've got to do it away from their parents, and you know, my understanding is that if they go and actually seek care to an STD clinic, then they're emancipated, and they can get it done there. So again, I just think we have to think a little bit more creatively about how are we going to get our 12-, 13-, 14-, 15-year-olds not just to be able to collect the specimen, but can we document that they can perform the test the way that we want it performed? And I like the idea, because I was wrestling with the group A strep and some of that, of doing it in a daycare center because you -- everybody there is able to give consent.

Thank you.

DR. PETTI: I agree with what's been said previously, and only add one population, and that's rural communities and perhaps teaming up with the rural health coalition or other rural-based practices. Individuals there are separated by large geographic distances. Sometimes it's 30 miles to get to a primary care provider, and they're a unique population that's often overlooked in clinical trials.

MR. WOLFF: Peter Wolff.

I agree with everything that's been said. Maybe I want to add a couple extra groups,

and those are people who have never tested positive for an STD, so that could be a question, you know, an inclusion/exclusion criteria: Have you ever tested positive for an STD before? You want low literacy --

DR. CALIENDO: I'm sorry, Peter, just to clarify. You would exclude them?

MR. WOLFF: No. So I would exclude people who have never had a positive STD.

DR. CALIENDO: Oh, interesting.

MR. WOLFF: I would want to include -- only include people who have tested positive in the past.

(Off microphone comment.)

MR. WOLFF: I think you're probably going to get more uptake from people who have tested positive in the past. It's a group that, I think, you'd have more benefit from. And then, so high school education or less, people who are uninsured, and then pregnant women.

DR. HAMMERSCHLAG: Okay, Maggie Hammerschlag.

I pretty much concur with everything. I think, you know, the way CVS is moving on to becoming a health center could provide a very good venue because people come in there with their sniffles, and they have a nurse there, and they do have probably a place where specimens can be collected, so that could be a site for a lot of this. I think that's pretty much it. The only -- well, I'll mention that, I'll talk about this other issue that comes later. At this point, just one thing: For these tests, are we just assuming, for the chlamydia and gonorrhea, that we are looking at genital only? Or are they going to be trying to do extra-genital sites? We haven't discussed that because that gets complicated. Whether the whole issue becomes --

DR. CALIENDO: Okay, so I'm just going to kill the extra-genital sites, and the reason I'm going to kill it is because we still don't have a laboratory-based assay for extra-genital

sites, so --

DR. HAMMERSCHLAG: Okay.

DR. CALIENDO: -- we're taking that right off the table.

DR. HAMMERSCHLAG: Which doesn't mean that people won't use it.

DR. CALIENDO: Not that it wasn't an interesting thought.

DR. CONENELLO: We can only agree that --

DR. HAMMERSCHLAG: Yeah, but it's --

DR. CONENELLO: -- once there is an FDA-approved test.

DR. HAMMERSCHLAG: But it may be used, unfortunately. That's another issue. Okay.

DR. NOLTE: Rick Nolte.

I'm thinking about this a little differently. I agree with every -- I mean, we all know who the populations at highest risk are for the various diseases that we've talked about. But I'm really -- the intended use, right? So these over-the-counter tests are really for people that don't take advantage of the current healthcare delivery system now, right? I mean, that's really the intended use? I mean, I'm looking for a little support here, a little --

(Off microphone comment.)

UNIDENTIFIED SPEAKER: One segment.

DR. NOLTE: Is it one segment, or is it really the laser focus of this? I mean, if people --

DR. CONENELLO: So in this case, what we're talking about when we say intended use is the FDA-approved intended use for the device, so where it says this is an influenza diagnostic for people between ages 2 --

DR. NOLTE: Okay.

DR. CONENELLO: -- and 70 for the detection of influenza, so not kind of the ideal

situation of who would be using this test, but the intended use of the diagnostic as written and approved.

DR. NOLTE: And I'm going to that latter thing. Who is likely to use this test? And it's likely to be the medically disadvantaged or disenfranchised, correct?

UNIDENTIFIED SPEAKER: No.

DR. NOLTE: No?

UNIDENTIFIED SPEAKER: Not necessarily.

DR. HANSON: This is Kim.

I think it's a lot about convenience.

DR. NOLTE: Okay.

UNIDENTIFIED SPEAKER: That's most of us.

DR. NOLTE: Okay. But I think there is a component of this, a subgroup of this, that we're really -- we're trying to bring people into the fold when it comes to sexually transmitted diseases. It's likely to be those people that don't have another easy means of access.

DR. BEAVIS: Rick, can I also say if you have a gal who's going to get the morning after pill, she's -- generally might be hooked in, but maybe, you know, it's people who have access to care but just want to be able to do some of this on their own, so I don't think it's only people who are underserved or don't usually go to doctors.

DR. NOLTE: But I think it's an important point of when you get around to looking at these tests, that you touch those populations.

DR. CALIENDO: Kelly.

DR. HENRICKSON: Kelly Henrickson.

A lot of great comments from everyone. So if there was -- I'll just comment about influenza. If there was going to be an over-the-counter influenza test, I would think that --

it is, I think, impossible to actually imitate the way it's going to be used for one important reason, is that we've done a lot of studies on the left and the right nose, and they don't match, okay? So using nucleic acid-based testing, and so you can't just do the left nostril and then say, you know, have a clinician do the right nostril and say that's a comparator test.

DR. CONENELLO: So that problem is more a problem with nasal swabs and mid-turbinate swabs than it was nasopharyngeal swab, so I would encourage any manufacturer to choose --

DR. HENRICKSON: Yeah. So my first recommendation is that you don't recommend nasopharyngeal or true nasopharyngeal because that -- to do a true nasopharyngeal, you have to reach all the way back and make them cough.

DR. CONENELLO: I meant for the comparator.

DR. HENRICKSON: No, I know, but what I'm saying is, is that for over the counter, the kind of swab that I'd recommend is a flocked mid-turbinate swab, which has been shown to have a fairly --

DR. GITTERMAN: If I could just comment. We're not going to recommend what the OTC does. I think Gina's point is critical. The comparator method has to be, you know, an approved FDA test in an ideal way. If manufacturers can do a nasal swab and show the performance is equivalent, that would be fine. I think it depends on the test design or the preliminary studies. We can't tell sponsors what to recommend as a policy. That's based on their test performance and what they've documented as data. So in an ideal world, if they can do a nasal swab and they could show it performed equally to the comparator test, which we look at as the referent standard, that will be fine. So I'm not quite sure what you're getting at.

DR. HENRICKSON: Well, I'm getting at that there's no way you can do a study for --

with a nasopharyngeal swab being done as --

DR. GITTERMAN: Well, if there's no way we can do a study, there will never be a product on the market.

DR. HENRICKSON: Well, I'm hoping it's not.

DR. GITTERMAN: Right. No, but --

DR. HENRICKSON: But there's been a lot of studies looking at nasopharyngeal swabs, looking at nasal swabs, and looking at mid-turbinate swabs, and there is decreased sensitivity and detection with a nasal swab versus an NP swab. But mid-turbinate swabs using the flocks, which has a bigger surface area, has been found to be fairly equivalent to well-done NP swabs, okay.

DR. CALIENDO: Kelly, we're not really going into a deep dive on the specimen type; it's more population, I think, is what they're aiming at, right?

DR. HENRICKSON: Okay. Well, my comment is, is that -- is how are you going -- you need to do these tests in populations, as you say, that represent how it's going to be used in reality, right? Okay. And so that includes all parts of the test, and so it's critical that you do -- there's going to be some comparison test, right, where it's compared of how the person's going to do it at home with how -- with a gold standard or something, okay. And so I suggest that that can't be done at home, okay, and it's difficult to do in the doctor's office, to try to reproduce that.

So I'm suggesting, sort of on some of Maureen's ideas, is that, you know, community centers for the elderly and daycare centers for young people are great areas to get two important populations of influenza if you have them set up -- what I'm concerned about is that it can't be a learning kind of thing; it has to be each parent has to or elderly person has to get their own specimen, right? Okay. And I don't think you can get two specimens that are the same, okay. I think it's very difficult to get two specimens that are the same for

influenza out of the nose. And so I think that the best -- my suggestion is the best way to do it is where the tester, the adult or the child who's being tested by the parent, does it, does the test in a separate room, you know, reads the directions, does the test and interprets the results, and then goes out and shows it to the person doing the study, and then they interpret -- and then they write down what they think the test result is because I don't think that you're going to be able to duplicate a respiratory sample.

DR. CALIENDO: Okay, again, we need to stay focused on populations that you're looking at. You mentioned --

DR. CONENELLO: Point taken, and we will take that into consideration because we have noticed those nostril differences, as well.

DR. CALIENDO: Okay, Lizzie.

DR. HARRELL: Lizzie Harrell.

I think we have some great ideas mentioned already as far as places to do studies, and I wanted to just make one comment, and that is to make sure that some of the clinics and schools and urgent cares or wherever we go includes unrepresented minority groups.

DR. MARTENS: Well, you know, I've done the studies with Dr. Van Der Pol and Dr. Gaydos, and I know that it's almost impossible to get a large number of gonorrhea samples, and it's going to be easy to get them in sex workers. But Dr. Beavis is right on the money because the question is to find ways to ensure the appropriate intended use populations are enrolled in studies. The 35-year-old sex worker knows exactly what's in her vagina and what's -- the 14-year-old, she won't even get the swab past her labia. So you need to enroll the patients that the label is going to represent. If you're going to test it in 15-year-old girls, you need to test 15-year-old girls to make sure they can do the test and collect the sample properly. If you're going to get a nasal swab, as you were saying, in a 75-year-old, you know, male with a deviated septum, you've got to know they're going to be

able to do it. In our studies, we collect the samples, so I can put a speculum in any age woman and get the right sample, but can she do it herself without a speculum. So I think we need to --

DR. VAN DER POL: We pretty much know where our vagina is before 12.

(Laughter.)

DR. MARTENS: Okay, all right.

DR. CALIENDO: Okay. So with that comment, so let's --

DR. MARTENS: I think sampling will be different.

DR. CALIENDO: Dr. Gitterman, let me summarize this question. So there were a couple of overarching comments about making sure we find -- enroll underserved populations, people of color, underrepresented minorities; make sure we go out into rural areas where people are often not included; pregnant women; and then some very creative ideas of where to do these studies. And so with the GC and chlamydia, we're talking -- we're trying to target high-risk teens and people in their twenties, looking at colleges, which may be our low-prevalence sites, and STD clinics, which may be our high-prevalence sites, using family planning also as a low-prevalence site; leveraging social media; asymptomatic and symptomatic.

We talked about the comparator, but I think this can be managed. I did testing for many studies in our school public health that were done in bathrooms in churches, very, very effectively self-collected vaginal swabs, so I think we can figure out the comparator. High schools, pharmacies, some good ideas on community outreach, sex workers, churches, nightclubs. Detainees are an interesting -- this all came under GC and chlamydia.

Flu is, I think, the group -- pretty much consensus, probably the most challenging because it's the most diverse patient population. You really have to go from children all the way through to adults and in a variety of settings. Nursing homes came up, community,

getting out in the community. I like the idea of shopping centers might be a good place. Daycare, urgent care centers will see a lot of people in the winter months.

And then finally, group A strep: daycare, schools, pharmacies, shopping centers.

So I think what you're hearing is get out of the typical places that you would do a clinical study, maybe do some of it, but going into areas that might be a little bit more out of what we typically use. And I think the group has given you some great suggestions. Anything you need clarified?

DR. GITTERMAN: Well, just actually a couple things. The first is I need to second what Gina had said. Whatever the intended use is, we'll have to ask that they be studied. I think a lot of what you're discussing is actually not oriented to FDA but is oriented to the manufacturers because what we're really discussing is enrichment to a large extent and not really sampling the intended use. Intended use population is almost impossible. Oh, excuse me. I made the same mistake you did. But encompassing the entire -- I made the same mistake Gina corrected earlier. Thank you. Encompassing the entire intended use population is almost impossible. How do you get people who wouldn't normally come to healthcare? To reflect the earlier discussion, people who wouldn't normally come for healthcare are not going to be coming to an STD clinic. I think the discussion was very interesting because the challenges to doing these studies are overwhelming.

And again, I think there's going to be a lot discussion, as to put a lot -- you know, this is sort of -- I hope it's a call to manufacturers to seek, you know, the expertise of people on this Panel, not necessarily, because that will make you a conflict for the next meeting, but, you know, getting experts in there because they're difficult studies to do, and there are practical limitations of getting every population at every -- you know, just as a background, our user requirement is three testing sites. It's very difficult to encompass all the populations you're talking about.

I do need to clarify one perhaps error and just make one other point. You could do a rectal or anal swab specimen. There's no prohibition against that. The barrier, unfortunately, is the bar is a little higher because that's never been cleared, and if you could do an OTC study over the way -- or, in fact, since -- you know, you could do a three-way study in a lot of ways, but I don't want to make this more complex. But the fact is if you could prove the device works against a comparator in the intended use population, we'll give it to you. As I mentioned before, it would be de novo, but there's no qualms about that. That would be very high bar, as Dr. Caliendo had mentioned, and I think her cutting off the discussion was wise, but there's no regulatory prohibition. You could do it.

The last thing is something which didn't come up, and I should have been a little more clear about the question. How do you feel, because again the bar you're raising is very high, about compromised patients? What about would you simply put a big black box in the label, because you keep talking about high-risk patients? Would we recommend OTC testing for high-risk populations, patients for whom the risk-benefit -- though the benefit-risk is going to be different. People who may be neutropenic or certain populations that may be at particularly greater risk, is that a concern given, again, they may be outside the intended use population?

I'll also make one last point. Asymptomatics are very likely -- very unlikely to come to these enrichment sites, and that would be another concern. And the last point is it was very, very interesting because the Committee has picked up on so much that when we talk about pediatrics, that's a specific regulatory intended use if you're looking at populations that are below adults. So that will have to be specifically justified. And it's an issue because if we have an OTC test -- you know, look at cigarettes were very, very difficult to restrict less than 18, and those might be -- so it's a very interesting discussion to do that and so -- but the one question I would ask, Angie, if you have any thoughts about --

DR. CALIENDO: Angie Caliendo.

So I don't feel, a priori, that we would eliminate immunocompromised patients at all. I mean, they are high-risk patients for influenza. So it wasn't my intent to mean -- to think that we were going to sort out immunocompromised patients and say don't enter these studies, because they may, in fact, derive some of the most benefit since they're going to end up being at risk for the most severe disease. And people talk about severe disease, I think they're in that group.

DR. CONENELLO: I just want to comment in terms of difficulty of study design. The FDA encourages manufacturers to come early and come often with Q-Subs, and we are more than willing to work reasonably with manufacturers to help design studies that are feasible.

DR. CALIENDO: Good news, we 're on Question 5. So why don't you read it for us, and we'll do our last lap.

DR. CONENELLO: Okay. Please discuss appropriate linkage to medical care should non-prescription over-the-counter assays for infectious diseases become available. Are there any recommendations regarding potential linkage to additional resources that diagnostic test manufacturers should be responsible for?

DR. CALIENDO: So we've talked about this a bit when we talked about mitigating risk, so I think we should think about what we haven't covered up to this point.

Mark, do you want to start?

DR. MARTENS: Sure. As you said, most of it has been covered. Dr. Petti answered it earlier; it was her question -- the earlier question. Yeah, I think a hotline is necessary. I think that the manufacturers, at least for the STDs, should have available a 24-hour hotline they can call. One of the things we haven't mentioned is it's 2 o'clock in the morning and you just found out you have gonorrhea; you're going to want to have something done.

Either a hotline or a website that links you to somebody, but when you -- or someplace, but if you call, they're not open. So now there's something, Zocdoc, and there are other, scheduling that at 2 o'clock in the morning, they can schedule an appointment for the next day. So I think maybe the manufacturers should look into automatic scheduling, also.

DR. HARRELL: Lizzie Harrell.

I don't have anything to add to that one.

DR. HENRICKSON: Kelly Henrickson.

I have nothing to add.

DR. NOLTE: Same for me.

DR. HAMMERSCHLAG: Maggie Hammerschlag.

I don't have anything to add.

MR. WOLFF: Hi, Peter Wolff.

One important thing to add. I think the CDC website needs to be listed. You can go to the CDC website, put in your zip code, and you can find a bunch of places to get tested and treated.

DR. PETTI: Cathy Petti.

I think, in the submission meetings, I don't know if we should entertain the question of data sharing, how you could share your test result with either your provider, the public health system.

DR. CALIENDO: So just to comment, Cathy, that came up in mitigating risk, was the whole public health reporting, that we think it may actually improve public health. So I think data sharing is actually a very important piece of this to actually -- that's a big hunk of the benefit that's come up over and over today.

DR. BEAVIS: Kathleen Beavis.

Nothing to add.

DR. RAND: Ken Rand.

Nothing to add.

DR. BEANAN: Maureen Beanan.

Nothing to add.

DR. GAYDOS: Charlotte Gaydos.

I think we've covered a lot of this before, but I would reiterate Barbie's comment earlier that to have each manufacturer have to have a hotline would perhaps be onerous, where people could go to ask questions or have counseling or know where to go to get linkage to care. I think package inserts for these tests should say next steps for the people that are negative and next steps for the people that are positive, about where to go or retest again frequently if you have these risk factors.

But I do think that the American Sexual Health Association might be one place that all manufacturers could use to perhaps not sponsor a hotline, but a warm line that would be maybe available from regular working hours, 9 to 5 or something, that people could go if they had questions. It would be a common place. And I agree with Peter that, you know, giving them access or a website, that they could go to CDC because there's a wealth of information on that website, too, for where they can go to get a confirmatory test or where they can find a testing site next to them. So the more we can help the individuals, the better off we'll be.

DR. VAN DER POL: Barbara Van Der Pol.

I have nothing to add.

DR. HANSON: Kim Hanson.

I would add one nice thing might be for the manufacturers to educate the vendors of the test as well, the pharmacists, because they would be another point to link to care and educate.

DR. DODD: Lori Dodd.

Nothing to add.

MR. SIMON: Tom Simon.

Just one thing. There are many patient advocacy organizations for the heart, the lung, cancers, and so forth, and there might be a place for patient advocacy organizations in this realm.

DR. PORTIS: Natalie Compagni Portis.

Nothing to add.

MR. KIMES: Dave Kimes.

Just two quick comments with 5a: That has to be the responsibility of the manufacturer and tied to the complaint management system, without a doubt. You know, safety can be monitored and perhaps facilitate future improvements. The other thing that might be an interesting consideration is that, you know, we talked about reporting results, yes/no. And these things can scan barcodes; why not the UDI? Maybe we can get some information that way about how the device is being used.

DR. CALIENDO: So interesting ideas. You know, what I'm kind of hearing is, is there a way to leverage the cloud or somehow get multiple -- you could even envision multiple manufacturers dumping data into the same database, getting to Cathy's point. I think the other point is a hotline that is a common hotline, leveraging our public health infrastructure so that every package insert -- I like what Charlotte said. This is what you do next if you're negative, this is what you do next if you're positive, and they're all dumping into it. The CDC's a very good, you know, thought.

Put in your zip code, I can find my closest CVS; maybe I can find my closest place to get STD treatment. I do think it would be ideal if it was 24/7. It doesn't necessarily need to manned, but if people could make appointments, I think we'd get more people into care

potentially that way. So centralizing resources, I think, Steve, it's not something that companies are traditionally doing up to now, but it may be a time to minimize. You've mentioned 10 times today, at least, the burden on the manufacturer. This might be a way to lessen the burden on the manufacturers while addressing a very important issue.

DR. GITTERMAN: I really appreciate the comments. Certainly something we heard very clearly is some mechanism, ideally across manufacturers, of having something available to bring to your physician. The issue again, a lot of these things are voluntary, and there's no way I think FDA can mandate them, and again, there's a lot of challenges. If you're negative at home, there has to be a mechanism to capture that. If you're going to your physician with a card, there has to be a way to capture that. No one will we be able to estimate -- you know, it's going to be a very awkward measurement, perhaps indirectly, if you have sales reporting and things like that, but again, manufacturers are often very loath to report that type of proprietary information. It's very difficult.

I do, with a smile on my face, Dr. Hanson, say, you know, when it's OTC, it may not all be pharmacies, and you know, educating the -- you know, the 18-year-old about -- you know, about how to do this on the counter at 7-Eleven may be a little awkward. I also have to smile to myself to say, as Gina brought up before, the comprehension of the reading level for a seventh grader. Well, some of the people using this test may be seventh graders. So we'll have to rethink that one.

But the advice, I think -- and I appreciate everybody getting us out early on the last question. A lot of this was touched, and it's a tremendous amount to think about, and I think one take-home message, and certainly if anybody disagrees with me, is that this may be bigger than any one manufacturer. It may take a lot of aspects of the public health thinking about this, coming out now because the community is very strong that they favor these types of things. A lot of the operational issues we can -- you know, we can address.

There has to be some way to address them. But some of these other issues of what's next, what to do, may be bigger than any one manufacturer. So I think the information we've been provided has been invaluable.

DR. CALIENDO: Anything else you need from the Panel?

DR. GITTERMAN: I would have to look at my colleagues, but I think this has been an absolutely invaluable day and --

DR. CALIENDO: You guys good?

DR. GITTERMAN: No, Uwe?

DR. CALIENDO: Okay, then we've come to that special time of the day. So I want to thank everybody. You did tremendous work. The Panel really stayed engaged for a very long and intense day and had great suggestions. Thank you so much for coming and being on your A game all day. I want to thank the FDA and the guest speakers and people from the public comments to have the interest to come and contribute to the discussion. I think we are done for the day, and the meeting is formally adjourned.

Have a safe trip home.

(Whereupon, at 5:15 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:

MICROBIOLOGY DEVICES PANEL

August 16, 2016

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____

ED SCHWEITZER

Official Reporter