SELF-COLLECTION DEVICES FOR PAP TEST PUBLIC WORKSHOP

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C O N T E N T S

P R O C E E D I N G S

MR. KALAVAR: Good morning. It's a little after 9:00 o'clock, so I think we'll get started. Good morning and welcome.

My name is Shyam Kalavar. I am a scientific reviewer, the Division of Molecular Genetics and Pathology, Office of In-vitro Diagnostics and Radiological Health, CDRH at the FDA, and it's my pleasure to welcome you all to this important workshop. We're looking forward to hearing your comments, feedback, from the different stakeholders in this room here, and I'm happy to see you all here.

To get things started, I'd like to introduce Don St. Pierre. Don is the Deputy Director, Acting Director, of Office of In-vitro Diagnostics and Radiological Health. I invite Don to say a few words.

DR. ST. PIERRE: Thank you, and welcome. As Shyam said, my name is Don St. Pierre, I am the Acting Office Director for the Office of In-vitro Diagnostics and Radiological Health within the

Center for Devices and Radiological Health.

So, usually my talk is really just about saying my title, and then I'm done, but today I'll do a little bit more.

So, welcome to this Self-Collection Devices for Pap Test Public Workshop. These workshops are really important to the FDA to get -- to hear from stakeholders and from all over the community. So, thank you.

We very much appreciate everyone taking the time today to engage us on this important topic, and for those of you from warmer areas, we're very happy that our weather has improved a little bit, hopefully making your travel to our home a little bit more enjoyable.

It's fitting that this workshop is -- related to cervical cancer is being held at this time, because January is cervical cancer awareness month.

Cervical cancer screening devices are really a major product area that my group has responsibility for, and as you all know, Pap

testing has made tremendous contributions to the field of cervical cancer screening.

We've assembled a group of inter-disciplinary experts in the field of cervical cancer, such as academia, professional organization, such as the American Society of Pathologist, the College of American Pathologist, researchers, practicing physicians, such as gynecologist, pathologists.

We have also a patient advocate who is a cervical cancer survivor, who will be taking part in the panel discussion session in the morning.

We have other stakeholders, such as manufacturers, who will take part in the public comment session in the afternoon, so I'd like to take this opportunity to thank my team for all their work in putting this workshop together, and making this happen today.

And for all the speakers and panelists that are actually taking time out of their busy schedules, and agreeing to be part of this dialogue, so thank you.

We hope to have a robust discussion on --

scientific discussion about self-sampling for the purpose of Pap testing, and we welcome comments and feedback on the -- from the different stakeholders on issues, on a variety of topics, such as benefit and risk of these products, feasibility and impact on the current established standard of care in the cervical cancer screening space.

We look forward to having a very productive meeting, and with that, I would just like to thank you all, actually, for coming today, and thank you in advance for your time, your participation, and most importantly, for your continued engagement in this -- on this important topic area.

So, hopefully, you'll have a wonderful meeting. I would love to be able to stay, but because of my title, I'm not able to. So thank you and have an enjoyable meeting.

MR. KALAVAR: Thanks, Don. So I think -- I'm not sure if everybody that's supposed to be on the panel for the morning session is here yet. I'm sure they'll show up. We're missing two,

actually; Dr. Cunkelman and Tamika Felder, but the panel session is not until later on, so we'll be optimistic.

Okay. So before we move on to the first presentation of the morning, I'd like to make some general announcements.

Some of these announcements you might have already seen in your email that you got as a confirmation for your registration, but I'll just quickly go over them.

Please have your phones, computers, and Blackberrys to silent mode. Wi-Fi access is available. The code is public access.

Food and beverages are out there available for purchase. There's also a bathroom back there.

Links to the archived webcast will be available on the workshop registration website shortly after the workshop, and the transcript will be available approximately 45 days after the workshop.

Here's some general announcements about the

meeting agenda. So, we've broken this meeting up into two sessions. The morning session, we'd like to talk about clinical considerations. The afternoon session will mainly deal with performance and validation considerations. We'll get into details such as a study design and clinical endpoints, and so on.

Now, each session will have presentations followed by a public panel session. Audience is encouraged to participate. Please ask your questions.

There's a mic set up in the aisle here; you can either walk up to the mic, or if you prefer to write you question on an index card, we can pass that to you and you can simply write your question on the card and pass it onto one of us; either me or some of my colleagues here.

Timekeeper, so Debu has agreed to be the timekeeper. So what he'll be doing is -- this is for speakers -- we want to, you know, try and stay on schedule here. We started a little bit late, but we'll try to keep on schedule here.

So, what Debu will be doing is he'll be holding up cards for when it's five minutes, two minutes, and maybe one minute. Right? One minute or thirty seconds.

Also there is a timer up here that will warn the speakers as to how much time they have left.

, the morning session, I'll be the moderator, and the afternoon session my colleague, Cheng Cui, will be the moderator.

Okay. So those are the general announcements. So, on to the first presentation of this workshop. It's going to be introduction and background, and what I'd like to do in this presentation is go over three main points.

I'll go over the meeting purpose and objectives. I'll go over the scope of the workshop, and then I'll give you a brief description of the regulatory landscape for cervical cancer screening devices.

Purpose for the workshop. So, basically, what we would like to do is -- we're trying to provide

a forum to discuss the topic of self-collection of specimens from the uterine cervix, for the purposes of liquid based Pap testing.

So, I'd like to emphasize three points here. Self-collection of specimens from the cervix, and that's the anatomical target for us, and it's for the purpose of liquid based Pap test.

We would also like to discuss -- we'd like to have a broad-based discussion about this topic, including clinical, scientific, technical, and even the programmatic aspects of it.

Self-testing; how is it going to be deployed out there? How are patients going to have access to these devices, and so on?

So, this meeting aims to discuss the feasibility and benefit, risks, of self-collection of specimens for Pap testing.

So, we'll have a discussion about does this really work? Does self-collection for the purpose of Pap testing from the cervix really work? What are the benefits, risks? Is there -- are there safety considerations for patients? We have

gynecologists here who will speak to that point.

Problems and current attitudes towards self-collection of specimens. Under what circumstances do women actually want to self-collect specimens for Pap testing? We'll have a discussion about that.

What are the attitudes of clinicians? Gynecologists? Will they have to change their practice, based on self-collected specimens? We don't know; we'll have a discussion about that as well.

Discuss the impact on current standard of care. So I guess it's safe to say that, at least in the U.S. we have a very good system of cervical cancer screening set up. What is self-collection going to do to this established standard of care? Is it going to benefit it? Is it going to be a disrupter? We'd like to discuss that.

Discuss potential intended use. , I'll discuss the intended use for these liquid based Pap tests in my upcoming slides. But is self-testing really going to stand up to an intended

use for liquid based Pap test? We don't know. We'll discuss that as well.

Discuss regulatory environment that will support self-collection of Pap test. Issues like performance; what is an expected performance? What is clinically acceptable? What are the study designs, validations, and so on?

Scope of the meeting. So, basically the scope of the meeting is self-collection of specimens from the cervix for liquid based Pap testing, and I'll go over what is out of scope; maybe it will shed a little bit more light on what we would like to discuss.

Self-collection of vaginal specimens. I think, based on the literature out there, self-collection from the vaginal -- if it's a vaginal specimen, then it's probably not going to work for a Pap test.

Self-collection for HPV. based on what you see in the literature currently, when you talk about self-collection, at least in the cervical cancer screening space, Pap testing is not what

comes to mind. We acknowledge that. HPV testing is what everybody thinks about.

But there's interest, emerging interest, that FDA would like to understand; that is one of the main purposes of having this workshop. We want to have a good discussion about self-collection for the purposes of Pap testing. Is it possible? Should we do it? What are the implications for a negative result? And so on.

Self-collection for other STD testing, such as chlamydia and gonorrhea. Again, that is microbiology testing, but -- and it's also a vaginal specimen, so that is out of scope of the meeting.

I'll briefly talk about the regulatory landscape. I'll tell you what the FDA has done with these devices.

currently there are two FDA approved cervical cancer screening devices. One is a Pap test system, and the other one is the HPV test system. And here are some salient features of these devices. They're both class three devices,

meaning they belong to the highest risk category, and as such, a PMA is required for these devices to be legally marketed.

It's regulated as a test system. So, we look at the whole system from specimen collection, all the way to reporting the result. And I'll go over the components in my upcoming slides. And these are both liquid based specimen collection.

And one nice thing about this liquid based collection is that a single specimen is sufficient for Pap testing, as well as a HPV testing.

So, when you collect specimens for a Pap test, it's from the cervix, and when the specimen is from the cervix, you can use it for a Pap test, as well as a HPV. But if it's a vaginal, it's probably not a suitable specimen for Pap testing, in most occasions.

Conventional Pap smears is a pre-amendment device. So, we're not discussing conventional smear. Pre-amendment device, what it means is it has been legally marketed before May 28, 1976, and for which there's no regulation requiring pre-

market application, that has been published by the FDA.

And also, I think, in the current cervical cancer screening space, most of the Pap testing is liquid based Pap testing.

So, here are the two approved devices for Pap testing, liquid based. One is the ThinPrep Pap test and the other one is a BD SurePath Pap test.

Now, again, they both have similar components. There is a slide preparation component, which is the ThinPrep processor, and that is a slide review component to it, which is the ThinPrep Imaging System.

Now, of course, the imaging system can be bypassed and these slides can be reviewed manually under a microscope.

Similarly, for the BD, the slide preparation system is the BD PrepStain System, and a semi-automated review is the BD FocalPoint GS Imaging System.

Now, there are several different versions of

these devices that have been approved, but this is the basic device that's approved.

General intended use. So, these liquid based Pap's are generally for the replacement of the conventional method of Pap smear.

Again, this is just general intended use for a liquid based Pap that FDA has approved. It's not specific to the specific device that I put up there, but this is the general idea.

And it's basically used in the screening for presence of atypical cells, cervical cancer, or it's precursor legions, like low grade or high grade SIL, as well as other cytological categories, as defined by the Bethesda System for reporting cervical vaginal cytological diagnosis.

So, the question is, at least for this workshop, would self-collection, for the purposes of Pap testing, will it be able to stand up to such an intended use? If not, is there an alternative pathway? We can talk about that.

So, here are the components of the liquid

based Pap system.

It starts off with the collection device. Usually it's a spatula, or a brush combination, or a broom type device. Again, the important point here is it's professionally collected.

It's collected, it's transferred to a liquid media, preservcyt, as in the case of ThinPrep or BD SurePath preservative fluid.

Pre-quot specimen. So, both these devices are approved for removal of a specified amount of a specimen from the liquid media for microbiology testing, before the testing for Pap.

So, then the Pap slide is prepared using the ThinPrep processor, or the BD PrepStain, as the case may be, and then the slide undergoes a manual review or a semi-automated review, based on what the system is.

Finally, the test report. Now, the test report is issued by the testing lab to the authorized clinician.

in this current scenario the specimen is collected by a professional; it's ordered by a

professional; it's submitted to the lab by a professional, and the test report is issued by back to the ordering physician.

So, it's a great system. there are good controls, it's well-supervised by physicians, and it works. So, we'd like to have a discussion about how this set up -- will it work for self-collection, and so on.

HPV tests. So this is the other approved cervical cancer screening device. Again, it has several intended uses. It's approved for primary screening for ages 25 years and older. It's approved a co-testing for Pap testing, plus HPV testing, for ages 30 and older, and for ASCUS triage.

So, for patients over 21 years old, and who have a diagnose of ASCUS, HPV testing can be done to assess the need for a cervical colposcopy, and we have several HPV approved devices on the market.

I'm just providing some examples of self-collection devices, just to give you a background

of what FDA has done with these.

Now, here's self-collection device for home use. So we have the FOBT kits for identification of fecal occult blood, and that's self-collected at home, and depending on the device, it's either mailed to the testing lab or or if it's a lateral flow immunoassay, presumably the testing is done at home. There are different kinds of devices. They're self-collected at the Doctor's office.

these are vaginal swabs for chlamydia or gonorrhea testing, and urine for chlamydia and gonorrhea.

So, the distinction I'd like to make here is self-collected at home, versus self-collected at the doctor's office. At least from the FDA's point of view, I'm not surethey could be considered equal.

We'll talk about this a little bit later on in the afternoon, because they're -- I think there are important differences, especially when you're trying to validate a device for self-collection.

So that's the point here.

Here's the references for the FDA approved cytology devices.

Again, so that's the end of my talk. What we'll do with questions is we'll ask the audience to please hold off on your questions, and we'll discuss your questions during the panel discussion session.

So, again, before I close, I want to stress we would like to have a discussion about self-collection for Pap testing. I know there's a lot to talk about self-collected for HPV, and there's not a lot of literature for Pap testing for self-collection.

That's one of the main reasons we're having this workshop, so we can get feedback from a panel like this.

So, I'll end my talk here and we will move on to the next talk. Our next talk is by Dr. Saraiya. And Dr. Saraiya is Medical Officer at CDC, and she's a captain with the Public Health Service,

DR. SARAIYA: Good morning, everybody. I want to thank Shyam and the FDA for inviting me, as a CDC representative, to talk on this issue, and my goal was to really talk about cervical cancer screenings. Sort of laying the landscape here in the United States, and I don't have any conflicts of interest.

So, you may have seen these vital signs, which is a CDC publication published a few years ago, highlighting that cervical cancer is preventable. We have 12,000 new cases every year, and 4,000 women die of cervical cancer, and it's felt that as many as 93 percent, at least 93 percent, could be prevented with a combination of screening and vaccination. Many feel that it could actually be eliminated now.

In 2012, even with our survey data, we were able to estimate that 8 million U.S. women, between the ages of 21 to 65, were not screened for cervical cancer in the last five years.

This is preaching to the audience, but you all know what cervical cancer is. In layman's terms,

it occurs when abnormal cells develop and spread in the cervix, and here we have a slide showing the virus infecting the epithelial cells.

I just wanted to also point out, in terms of where cervical cancer strikes, it's often where this squamous cell -- where there's metaplasia between squamous and glandular cells rising -- giving rise to squamous cell cancers, and then the glandular cells giving rise to adenocarcinomas, which will be important because almost a quarter of cervical cancers are adenocarcinomas in the United States.

This is a natural history model of cervical cancer, and I know many of you have seen different versions of it, but briefly, just to go over that there's a normal cervix, and then there is an HPV infection.

Many times, the HPV infection in green can clear back to normal, but it's the persistence of HPV that leads to the progression of pre-cancer and cancer, and usually there's a, median of ten to fifteen years between those steps,

in green, red, and blue.

On the bottom are risk factors, and the risk factors are sort of highlighted and placed, in terms of where the risk factors for.

So, there's risk factors for acquiring HPV. Usually these have to deal with age of first intercourse, the number of sexual partners, condom use. Then there's risk factors of what leads to pre-cancer.

These risk factors have been identified, and mostly have to do with whether the HPV can clear, or not. Long term OC use, smoking, multi-priority, as well as the type of HPV, and then what leads from pre-cancer to cancer has a lot to do with the type of HPV.

We really don't have, in the United States, as opposed to other organized screening systems elsewhere, we really don't have a registry for pre-cancerous lesions, so the best we can do is estimate.

It's estimated that we have 1.4 million cases of low grade cervical dysplasia, or CIN-1, and

330,000 new cases of high grade cervical dysplasia. And, as you can see, the references are a little bit old, but we still use them.

We do have a very robust cancer registry in the United States. Every state has a cancer registry now, in the United States, including Puerto Rico, and so we're able to, sort of, figure out where cervical cancer is, and we know from there, that until 2014 that's the -- there is a lag time between when real cancer data are available and the current time.

We have around 12,500 new cases of cervical cancer, and 4,100 of cervical cancer deaths.

And here there's a map. It's a little bit misshapen, but you can see here in red are where the highest rates of cervical cancer are in the United States, and these rates are -- so the average is 7.5 per hundred thousand in the United States, and these in orange and yellow are above the average.

So, you can see a lot of the central states, such as Texas as the Alabama, those have such high

rates, as well as those states with Appalachia, like Kentucky and West Virginia, and then also Puerto Rico actually has one of the highest cervical cancer rates in the United States, with a rate of around 11.7 per hundred thousand.

This map is basically looking at it at the county level. So, here what I wanted to point out here is that there's those red pockets where cervical cancer is really quite high, and if you look at it, almost every state has a pocket. States that have a large enough population, and these most likely are rural areas, but also some urban areas where there's just a high population that has not been screened.

So, maybe in Texas, for example, or in parts of Florida.

In terms of cervical cancer rates by demographics, I thought it was important to show that what racial ethnic groups has the highest cervical cancer rates.

Right now, it's Hispanic populations, as well as African American populations, that have the

highest rate of cervical cancer. 9.4 per hundred thousand for Hispanic population and 8.5 per hundred thousand for the African American population.

While the other groups have lower rates, I think it's important for us to remember that if you actually parse it out by specific age and sub-groups, there maybe some age and sub-groups that actually have higher rates of cervical cancer, but we're sort of lumping them right now.

And then in the slide next to it, we look at rates of new cancers by age group. And here, you know, the median age of cervical cancer diagnosis in the United States is in the early 50s.

Here you can see where the peak -- some of the peak bars are. You see a lot of cervical cancer occurring -- really, it's quite rare under 20, very few cases between 20 to 24, but most of it is in 40-44, 45-49, and 50-54.

So, that's why it's important when we speak out interventions -- this is a nice slide that looks at HPV vaccination and screening, and then

you have the overlay of the green graph that looks at when HPV infection is at its peak, when high grade cervical pre-cancer, such as HSIL occurs, and when cancer occurs, and you can see the HPV vaccination is currently targeted between the ages of 11 to 12 year olds, prior to when HPV infection would actually occur.

And screening is occurring a little bit after, at age 21, and I'll explain a little bit about the rational.

So, what do U.S. screening guidelines say? Well, first of all, there's many screening groups that have screening guidelines in the United States.

But cancer screening, it's important to highlight that we're talking about looking for cancer before a person has symptoms for cervical cancer.

That means that there can be an earlier stage of cancer, and easier to treat, and then specifically for cervical cancer we can detect pre-cancer, similar to colorectal cancers.

And abnormal screening results do need a

follow up to confirm the cancer. So, we're talking about diagnostic testing. So, it's important to remember that when we're talking about screening, we're talking about asymptomatic populations, and not somebody who has symptoms.

The Pap smear has been around since the 1940s. Developed by George Papanicolaou. It's one of the most common cancer screening tests, and it's been introduced as a key part of the annual gynecological examination, and I still hear many women who are not able to -- you know, where it was linked to contraceptive care, as well.

So, that's why we were able to get this annual screening as high as we were, because it was linked to many of the fundamental annual visits that were required of women, and it has greatly reduced cancer mortality in the United States.

A Pap test, or smear, looks for changes in cells or cervix that could turn into cancer, and as Shyam alluded, that almost 85-90, maybe even higher, 95 percent of cervical cancer screening occurs through the liquid based Pap, as opposed to

the conventional Pap.

And in the breast and cervical cancer screening program, which the CDC supports, almost -- we would have, maybe 85 percent is mostly conventional liquid based Pap, but there are a few pockets in North America that still do conventional Pap.

The HPV test that Shyam mentioned looks for a virus that causes the cell changes. There's many that are out in the market, and co-testing is a combination of the Pap and the HPV.

So, there's three organizations that recommend cancer screening, per say, cancer screening in the asymptomatic population. That's a U.S. Preventive Services Task Force, federally appointed panel of independent experts.

The American Cancer Society often is linked with the ASCCP and the ASCP, and they convene expert panels.

The American College of Obstetrics and Gynecology, they usually publish a practice bulletin in gynecology.

So, in 2012 -- this was probably the first year where there was alignment of all the guidelines.

So prior to 2012, there would be a little tweak here, a little tweak there, and generally the -- in 2012 the age to start was agreed upon, age 21, and that had a lot to do with that natural history slide, and the curve I showed you, that often HPV infection is thought to occur as soon as women is sexually active. It can regress. And being really proactive in aggressive screening in younger populations may lead to some reproductive health harm.

So, there was an agreement that age 21 would be the screening age to start, rather than based on onset of sexual activity.

And I must say, when I've looked at guidelines -- when we've looked at guidelines, and what's being adhered to the most, we would say that this is the -- one of the guidelines, the new guidelines, that everybody seems to be in agreement with, and you see a significant drop I

women under 21 being screened.

Women ages 21 to 29, generally the consensus is cytology every three years, and women 30 to 65, there was a choice between co-testing every five years, with the HPV and Pap, or every three years with the Pap alone.

Consensus, again, on women older than 65. Discontinue if they've had an adequate negative screening, and that was defined by either certain number of pap tests, or HPV tests, in the past 10 years.

Then post-hysterectomy, there's definitely agreement that if hysterectomy has been done for benign reasons that we can stop screening.

So, since 2012, after the FDA approval of a primary HPV test for -- HPV test for primary screening, the ASCCP, ACOG and American Cancer Society came out with interim guidance where they approved, basically, the same indication that the FDA had. The primary HPV test can be considered for women starting at age 25, is one of many screening options.

So, they weren't saying that it was preferred, but it was one and -- one of many options. Women with a negative primary HPV test should not be retested again for at least three years, and then they actually provided some guidance on a positive HPV test, especially for 16-18, was associated with a higher risk of future disease, so there should be an immediate -- should be followed colposcopy, as well as those that were HPV positive for other types that were in the HPV test, should be followed with cytology testing.

Then ACOG, in 2016, came up with guidelines, and they basically confirmed their 2012 guidelines, but what they added this time was that they added risk groups.

Where most of the previous groups, sort of, speak about average risk group, the ACOG identified a low risk group; again, women who have had a total hysterectomy and no prior CIN-2, that there shouldn't be any screening, but they also went above and beyond and highlighted high risk groups, and these are the guidelines.

That HIV infected women, immuno compromised women, and DES exposure, they have a little bit more screening that's occurring; either screening occurring earlier than 21, and occurring more regularly.

In 2017, the USPSF issued some draft recommendations. I don't think these have been finalized, and they're finalizing -- there's been a period of public comment, that many organizations provided comment on, but it's a real game changer if it does happen, in that for the first time they're saying continue with cytology every three years for women 21 to 29 years, and then for women 30 to 65 years, they're doing away with co-testing. It's no longer recommended.

They're saying HPV test every five years, or cytology every three years, and this was based on a review of the evidence, as well as modeling, as well.

Then age 65 is similar to what it was in the past, that adequate screening history, you can stop.

So, I often use this cartoon in our talks, in terms of what test will be on the menu and what test will you have? Where two women are -- and the bartender is maybe the provider, but maybe the provider isn't asking. So, I think it's -- you know, every three years; I prefer the HPV and the Pap test every five years; or I prefer the HPV test alone every five years.

I think it's really important because I did, sort of, an ad hoc Facebook query yesterday with my colleagues, with my friends, with my Facebook friends, many of which are OB/GYN's, and it was really interesting to hear from women, in terms of what they said. They were very interested in the idea of self-collection; not going to the office.

And then my provider friends were very concerned about self-collected, and especially they raised many of the other issues that we've had about frequent screening in general. Like, what do we do about the bi-manual exam?

So it was like, well, let's stick to the topic area, and that's why I vow never to discuss these

issues on Facebook again. Because it definitely raised some interesting comments.

But, seriously, going back to the 35,000 foot view of cervical cancer incidences and mortality, just wanted to say, again, that Pap based screening has resulted in decreasing mortality, as well as decreased incidences. Then we have that -- in 2004 when HPV enhanced screening was started.

I think we've sort of reached and saturated how much impact we're going to have, and I think the benefit of HPV enhanced screening is multi-fold, in terms of using a safe interval. You can extend the interval, the negative predictor value, and all that.

But I would want to say that what really impacts cervical cancer incidences and mortality is coverage, coverage, and coverage. Location, location, location. And, of course, seriously, follow up of abnormal tests.

In the United States we, again, don't have a registry to really tell us how many women are

getting screened every so often, so we use survey data, and survey data, if they're done well, and done consistently, do allow us to look at trends, and we see that 83 percent of women are screened in the past three years with a Pap test.

So that is -- that's the top line here, and then you see mammogram and colorectal cancer, as well.

So, you can see that generally it's been stable. If it's going down a little bit, it's usually been because it's gone in the women under 21, which we have measured over time, and then that -- but there are a few women that -- there are women who are not getting screened.

Who are the women that don't get screened? And this is based on several data sources. These are women, usually, that are lower educated, underinsured, specific racial ethnic groups. Well, as I mentioned, specific Asian subgroups, American Indian/Alaskan Native, Hispanic, specifically coming from these countries, Mexican, Mexican-American.

Foreign born women are significantly less likely to be screened, especially if they've been in the country less than ten years.

Sexual orientation can impact a women's comfort, and her risk level of being screened. Certain religions can have barriers, in terms of women expressing concern about male providers, or being unclothed. As well as rural and geographic barriers. As we've mentioned, Appalachia, the U.S. Texas boarder, and what is part of the United States, the Pacific Islands, as well.

So, this is a slide from my colleague, Dr. Hershel Lawson, who used to be at CDC, and this is data from 1995, mostly using data from a managed care group, and this is where we come up with that data that 50 to 60 percent of cervical cancer occurs among women who've never, or rarely, been screened. And by rarely, we mean in the last five years.

So, we have 50 percent that are never screened, and ten percent that are rarely screened.

And what factors then contributed to cervical cancer cases? Besides not being screened, were women, five to ten percent, that had a false negative cytology test, because that was the test that was predominantly used then. Ten to fifteen percent where there was loss to follow up. Ten to fifteen percent where the cytology cytology not abnormal and was mismanaged medically. Five to ten percent were rapidly progressive cancers, and nine to twelve percent where the cancers were difficult to detect by a cytology test.

So, specifically, there are a few cancers that have been difficult to detect by cytology test. We often think a high proportion of these are adenocarcinomas.

Then there's a proportion of cancers that are rapidly progressive. Neuroendocrine, for example. But it's also been found to be HPV positive.

Now, we fast forward to 2017 publication by Phil Castle, et al. Again, they looked at a managed care organization, looking at 623 cervical

cancer cases among women who had a co-test from 2003 to 2015.

If you look at the pie, 58 percent of cancers in the managed care organization were considered prevalent cancers. That by the time the woman had the co-test the cancer was already in place, prevalent, so it's mostly attributed to a screening failure.

Then there were several ones where there was a false negative cytology or HPV test, false negative histological diagnoses, where there's non-compliance, either through screening or management, algorithm delays, or treatment failures, per say, of the cancer.

So, I think the point here I wanted to make is that we still think that a significant proportion of cervical cancers that occur here in the United States are among women who have not been screened, or rarely been screened.

And these are both managed care organization graphs that I show you, so you can only imagine in a public health system, I would imagine that that

proportion is higher.

In fact, in Spain and England where they have an organized screening program -- or in Spain -- in England they have an organized screening program; they have found similar kind of proportion, and in Spain they found that the proportion of women who are getting cancer, who have not been screened, or not screened regularly, is around 75 percent.

So, I'm coming to self-collection. Probably violated Shyam's suggestion to limit it to Pap testing.

But self-collection for HPV testing is all I can really speak on, in terms of what the literature is, and can it increase acceptability, and I think it would be important to know -- I know we're going to hear a little bit more about actual rigorous reviews that have been done on self-collection, but on my initial review of the literature, it can increase acceptability.

It removes a need for a speculum exam. It removes the need for a clinician for initial

screening, so the services can really focus on follow up, whether it's at the home, the community center, places of gathering.

It can be combined with other self-collection tests that may be done at the same time for women that are at high risk, or younger women, such as chlamydia and gonorrhea.

There has been a lot of work done in the low resource settings, but there's also been pilot studies that have been done in North American showing high acceptability, such in Appalachia, Kentucky, the black women in Mississippi, Somalian immigrants in Minnesota, as well as Hispanic women in North Carolina.

But there do remain a lot of unanswered questions. For example, does it actually lead to screening rates at a population level? Because most of the work that we've done -- most of these studies have been pilot studies -- and does follow up increase as a result? Like, will the women who are non-screeners actually follow up with their abnormal result?

I wanted to just briefly comment on HPV vaccine impact on screening, as we think about the future.

Obviously, the vaccine, even with the low coverage -- low, but slowly steadily increasing coverage here in the United States, will decrease HPV infection, pre-cancers, and we now have a study that shows that it can -- it does decrease cancer.

We have found in the United States that there's been a 64 percent decrease of HPV infection, pre and post HPV vaccine, in the youngest age group, and that's at a less than 50 percent population vaccine coverage.

Studies have shown a decrease in pre-cancers, mostly in Australia and Denmark, where there's been higher vaccine coverage, and as I mentioned, there's been one recent cohort follow up showing a decrease in cancers.

So, the screening, because -- will need to be more HPV based, and definitely can be even later and less frequent that it's -- than it is now.

In fact, in Australia, which is what are other countries doing, I wanted to just briefly talk about Argentina. Argentina has had a pilot study where HPV based screening was used by community healthcare workers, where the uptake increased from 20 percent to 86 percent.

Guatemala and Nicaragua are introducing HPV, including self-collection.

The Netherlands are planning to have HPV based screening, and they will be selecting -- doing self-collection of HPV based screening to non-responders.

And, as I mentioned, in Australia, they have been able to switch from an 18 year -- starting to screen with Pap only every two years for 18 years old, to an exclusively HPV based screening starting at age 25 and occurring every five years.

And, you know, they say privately that they can see where -- because they have such high HPV vaccine coverage that women may need to be only screened once or twice in their lifetime.

And they're definitely considering self-

collection as part of their rollout for non-responders.

Even in Africa, in Uganda, from a pilot study, the uptake rates have been greater than 95 percent, compared to 48 percent for VIA.

What I failed to mention is that USPSTF draft recommendation, actually alludes to self-collection being a very promising strategy, but they didn't have enough data to, sort of, talk about that, especially here in the United States.

So, in summary, cervical cancer is decreasing, but it's very preventable with the tools that we have in hand. Coverage has been stagnant for several years.

Screening guidelines are moving towards HPV based screening. Screening occurring at later ages and less frequently, and the HPV vaccination has the potential to change those even more.

Self-collected, however it's actualized, can improve coverage.

Thank you so much.

MR. KALAVAR: Thank you, Dr. Saraiya.

So our next talk is Dr. Staats. He's the Associate Professor of Pathology, University of Maryland.

DR. STAATS: Thank you, Shyam, for inviting me. It's a pleasure to be here today.

So, I am Associate Professor at the University of Maryland, School of Medicine, and I am a practicing pathologist and cytopatholgist. I'll be talking about the topic of self-collection of cervical samples, approved cervical cancer screening, and spoiler alert, the answer is going to be I don't know.

So, I have no specific conflicts of interest to disclose.

This is -- this background is a little redundant, with Mona's very nice presentation, so I'll be brief about it.

We've seen about an 80 percent reduction in cervical cancer in the United States since 1955. This is driven primarily by Pap testing.

It's moved from the number one to number 14 cause of cancer death in the United States, but

remains a relatively common cancer, nevertheless, with about 12,500 incident cases in 2014, and 4,100 deaths in the United States.

The HPV vaccine and HPV DNA testing have important roles, but Pap testing really remains a cornerstone of prevention, either as primary screening, or as an important component of HPV primary screening. It remains part of the algorithm.

So, again, cervical cancer remains being a killer. Worldwide about half a million cases and 250,000 deaths annually. In the United States, obviously, where there's -- and in general, in countries where there's a more developed screening program, the numbers drop significantly, and we talked about the numbers in the United States.

But I put them here again to emphasize that that's still a lot of cases and a lot of deaths, and certainly we're still -- we still could be doing a lot better, in terms of preventing cervical cancer in the United States.

The majority of cases, as Mona just very

nicely demonstrated, are in women with insufficient screening.

So, there are access issues, both in developed world, and especially in the developing world, and the most prominent of these is a lack of insurance, otherwise lack of access to care.

Other important features that are commonly indicated as reasons not for getting Pap test include lack of health information, not understanding what cervical cancer is, what the Pap test is, etcetera, etcetera. Practical barriers, language barriers, distance to clinics, unavailability of a clinic nearby, childcare, etcetera, etcetera.

Various personal beliefs, as well as generally fear of the medical community, or fear of specific issues regarding this testing.

So, you could see, as you look through that list, that self-collection at home, potentially, could be -- get around a lot of those issues. Potentially could be valuable in reaching some of those women who are not currently being reached.

Yes?

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. STAATS: Oh, sorry. I didn't realize we weren't. Absolutely.

So, there are quite a few studies on self-collection devices; the vast majority of them are focused on HPV. The number of studies on Pap testing, specifically, are relatively low and tend to be relatively small-scale studies.

They use a variety of methods and devices, including swabs and brushes, similar to what's used in provider collected Pap's, as well as techniques like lavage or tampon.

Most of the studies show pretty good sensitivity for HPV DNA testing, when compared to provider collected tests, but most of this testing that has looked at cytology has found relatively poor sensitivity compared to provider collected tests.

There's a reference down below to a review article on self-collection devices that you can look at if you're interested.

More show -- so again, mostly vaginal cells are what's being collected, not cervical cells, in most of these testing, which maybe suitable for HPV testing, where you're looking for an infection, which is going to affect a number of cells throughout the gynecologic track, potentially. More challenging for cervical cancer detection, where you're looking for specific neoplastic cells that have to come from the actual legion.

So -- good, this shows up better for you than it does for me.

Women, potentially affected by self-collection. So we talked about the number of women who are getting cervical cancer screening. There's various numbers, but just for simplicity, we're going to say about 85 percent of women get -- have had cervical cancer screening within the last five years.

Some of the issues with data that's collected by the government is that it focuses on did you have a Pap in the last three years, with now

screening intervals taken out to every five years, it makes some of that 83 or 81 percent that was just shown a little bit artifact of the changes of screening intervals, as well as the issues that were already talked about with 18 to 21 year olds being included because of prior screening guidelines.

So, anyway, I think 85 percent is a fair baseline estimate. So, that means about 15 percent of women have inadequate screening.

Now, so we talked about some of the causes; lack of insurance, no primary physician, health information, practical barriers, personal beliefs, fear.

As we talked about, you can imagine that this would have some help with that, but only limited help really.

You know, if you look at somebody with a lack of insurance, for example, which is the most common issue with inadequate screening, typically, is that if you price this device low enough that they can buy it themselves and do the test

themselves, then maybe you get some of those women who otherwise can't afford to get Pap testing, to get their Pap testing.

Can those women now afford to go to a doctor to follow up on an abnormal result? When we look at this issue -- all these issues, our goal is not to get this 15 percent of women Pap tests, our goal is to get these 15 percent of women testing and treated appropriately so that they do not develop cervical cancer.

If we give them an ASCUS diagnosis or an HSIL diagnosis, and they do nothing about it because of fear of the medical community, because of practical barriers to reaching care, because of a lack of insurance, we've done them no good whatsoever.

Now, there are going to be some women who make these decisions on the margin, who are going to be shifted by the fact of an abnormal result, into going and seeking care.

So there will be some -- there would presumptively be some advantage, but we have to

make sure we're not, sort of, using getting a Pap test as a proxy for actually improving these women's lives.

Getting a Pap test does nothing to improve their lives; it's getting treatment for their potential disease that does.

So, now, these women -- we talked about some of the various socioeconomic, and other features of these women in the last talk, and so as you look at that list, they would be a marketer's nightmare, in terms of trying to reach these people.

They're people who tend to have lower socioeconomic status, lower educational levels, etcetera, etcetera. These are going to be hard people reach and to target.

The fact that many very intelligent, very hard-working people have spent decades trying to get as many of these women as possible into screening, and we still have a 15 percent, or so, of women who can't get there, tells you these are very hard people to reach.

So, let's be wildly optimistic. Let's say half of these women you suddenly get, not only Pap tested, but actually get them, as necessary, into further management and treatment of their disease. That's 7.5 percent; half of 15.

Now, let's look at the women who are currently getting cervical cancer screening. Some of those women might decide they like better doing it themselves and not going to their doctor.

In fact, there's some literature on self-collection. There's a recent meta-analysis that looked at actual patient attitudes who have done self-collection, and found about 60 percent of them prefer the self-collection to physician collection.

Now, you know, if you want to market a self-collection device, that's a very good statistic. Great. But you know, you don't want to try to create a device that nobody wants to use, so that's good.

But that means that some of the people who are currently going to their doctor for screening, may

decide they'd rather just do it themselves at home. They'd rather skip that physician's appointment; they'd rather do it themselves at home.

Let's be a little less optimistic about how many women are going to switch, and say only ten percent of women decide they're going to do it themselves. Right? So that's ten percent potentially harmed by a test that's less sensitive, if it is demonstrated to have -- if it's not demonstrated to have equivalent sensitivity.

So, you know, let's just overlay these circles to make them easier to see. You can see that fairly easily, using fairly conservative assumptions, you have a larger number of women who are potentially harmed by this device than are potentially helped by this device.

So, I think what we're -- what I'm saying with this very long slide, is that we need to make certain that this -- any of these devices that are brought to market need to be very much as a good

as the existing Pap test, and if we can't demonstrate that then it's probably not safe to bring it to market.

So, some more specific issues on self-collection from the lab perspective. I'm going to break this into specimen collection and transport, choice of lab, laboratory interpretation, result reporting, and follow up of results.

So, specimen collection, we'll start with. This, I think, is another really key point. My second major key point of this talk.

This is a diagram of the actual anatomy of the cervix. You can see -- so here's the entrance of the vagina, and you can see the cervix way up here in the back, kind of point away from where you'd want to stick your self-collection device.

The place where the vast majority of cervical cancer occurs in a little tiny area right here at the cervical Os, call the transformation zone of the cervix.

So, you've got to -- and again, we're talking about actually sampling dysplastic or cancerous

cells. We're not talking about some field effect where you're going to be able to see some changes in a cell down in the vagina to make a difference.

What you need to do is sample that little area right there. So you need to make sure that this device is actually capable of getting there, and that's going to be a challenge to get there.

So, this narrow little transformation zone of the cervix, is really what the women is going to be targeting, if she's self-collecting.

Clinicians have guidance in using a speculum exam, where they can actually see what they're targeting, and target the specific area in most patients, but obviously, if you're self-collecting you're not going to have that visual assessment. It's going to need to be a device that can reliably get there without visual aid.

Obviously, materials have to be safe for patient use. The existing ThinPrep vials have, primarily, methanol as a preservative. Methanol is not a very safe thing. It's a very small quantity of it, but it needs to be -- it's

something that needs to be looked at. The Sure Path, which is a less common one is primarily ethanol based, but has a small amount of methanol in it, as well.

Both of these are not only -- so the methanol is certainly not safe for consumption, it's also -- both of them are very flammable.

So, there are some issues when you're sending this vials home with patients. Again, they're small vials, so they can probably be overcome, but there are some issues that need to be looked at.

If -- is liquid based cell preservation device being used, then it has to be transportable, so again, current preserve site and Sure Path recommendations, that they be stored both before the cells go in, and after the cells go in, at room temperature, which is defined in the MSDS as 15 to 30 Celsius, or about 60 to 85 Fahrenheit.

You know, anybody who is here in -- anywhere on the East Coast, basically, for the recent cold snap can imagine that probably some of the FedEx trucks that these specimens might be going in

might well be a little bit below 65 Fahrenheit, and anybody who's been through a D.C. summer, or a whole lot of other areas in the country, summer, knows that 85 might be a little bit lower than what transport might happen.

So, it would be important to evaluate that. Not that, necessarily, those numbers are critical to the test result, but that needs to be evaluated.

Then the lab needs to have a way of knowing whether these are compromised specimens. So, again, you know, the existing recommendations for ThinPrep and Sure Path are a certain number of weeks after specimen collection that it needs to be tested.

Is there a way to know when the patient actually collected the specimen? Did they collect it and then forget it in their medicine cabinet for two months and then send it in? Is that now an acceptable specimen, or has it been compromised? Is there going to be any way for the receiving lab to know that information? So there

needs to be some thought on that, for example.

You know, there are obviously compromised specimen issues that exist currently, that would continue to exist; leaky vials, and various things of that nature, will continue to exist.

A little bit on choice of laboratory. So, there have been some tests that affect pathology that have been brought to market that have used a model of, sort of, a specific partner laboratory, where all of the testing done by a specific device goes to a specific laboratory.

We, in the pathology community, I think I can safely speak for pathologist as a whole, or not, not thrilled with that sort of arrangement.

We think for patient -- patients should have a choice of where they have their lab testing done, and should be able to -- and I think it's going to be valuable, in terms of patient satisfaction, and in terms of quality, that that be an option

So, I think labs can then -- if you allow -- if you set up a system where there's a single lab that these go to, it creates a suboptimal

situation; whereas, if labs are competing for business, on the basis of things like pricing, turn around time, and quality, you're likely to get more patient satisfaction and better quality of care.

So, lab interpretation. This almost, at first, seems like the most straightforward part, if you're creating a device that collects into an existing medium, then probably the interpretation is going to be about the same, you would think at first, but maybe not so much.

So, if you're -- obviously, if you're collecting into a different sort of medium, you're potentially creating a variety of fixation and preparation artifacts, that potentially lead to a whole different way of interpreting that Pap test.

It's not like the cells are magically the same, no matter what you put them in. So what you put them in makes a big difference.

So, if somebody's going to try to bring to market something that uses an existing medium, then that's -- those fixation preparation

artifacts are less of an issue. But if not, then additional training for pathologists might be necessary, and perhaps changing in criteria for how diagnoses are made are going to be necessary. So that needs to be evaluated.

Then, I think, a really important thing is even if you're doing a similar liquid based preparation, there might still be need -- necessary for modification, particularly, with adequacy criteria.

We talked about that transformation zone of the cervix is a very small, very difficult to reach, area. When the initial Bethesda System came out, endocervical cell sampling was required for an adequate specimen, and that's because, knowing that the transformation zone is the area where the cancers happen, if we can't see that on the slide, we don't know that clinician has actually collected specimen from the right area, and so we consider that an unsatisfactory specimen.

Over the years, studies were done that

demonstrated that actually the rate of false negatives in patients who didn't have endocervical cell sampling identified, was actually about the same as it was in women who did, and so we've eliminated that in more recent additions of the Bethesda System.

But all of the studies were done in patients who were provider collected under direct visual sampling. If you're now having the patient self-collect without visual sampling, the lab is not going to know whether that's a vaginal introitus specimen, or whether that's a cervical specimen, unless they see endocervical cells.

So, we may need to look at whether identification endocervical cells actually is a requirement for an adequate specimen, and it's going to require a fairly large-scale study to evaluate whether that's the case.

And if that's not hard enough, this I think, is actually the most challenging part. If you're going to reach that 15 percent of women, it can't be done by saying you have to go to a doctor, and

collect it in a doctor's office.

If you're going to go to the doctor and collect in the doctor's office, then you're providing not additional value, whatsoever, in terms of reaching those patients who currently are not screened.

If you're going to require that they list a doctor on that form, and the results go back to that doctor on that form you're, again, providing no additional value for any of those 15 percent of patients.

So, if you want to try to argue that you're going to provide value to that 15 percent of patients who aren't reached, it has to be done by the patient, sent by the patient directly to the lab, and reported back by the lab to the patient, and that creates a whole lot of issues that the labs are currently not really set up to deal with.

So, if we report directly to the patient, it potentially is patients -- you know, can imagine your lab calling you up and saying, you have squamous cell carcinoma, you should find a doctor

and go see him. That's kind of awkward. It's not really good patient management, in the way that we currently understand it.

So, patient is potentially left holding an abnormal result, but without a way to act on it, because they don't have a known doctor, and they have to find a doctor somehow and figure out what to do about it.

Also, our typical reports are really targeted currently at physicians, at clinicians understanding of what we're saying, and so we use terms like, for example atypical squamous cells of undetermined significance.

If you, as a patient, gets a result that says atypical squamous cells of undetermined significance, do you know whether you're supposed to go see a doctor about that or not?

So we need to make sure that -- the reports would have to be generated in a way, if they're going directly to patients, that is very clear on exactly what that means, and exactly what the patient is supposed to do with that, and if not,

we're going to have potential issues with inappropriate follow up of those results.

Then, of course, there are language and literacy issues for a lot of these patients. So, if you can't read your report, it does no good that your report tells you it's squamous cell carcinoma.

So, if the patient designates a physician, and then as we talked about, those most in need of testing aren't going to have a physician, and so that's not really going to provide them any value.

So, if you're targeting the patient, or even a responsible physician who you don't, as a lab, have an existing relationship with, and you can't get the result to them, you can't find them, the patient does -- you know, the patient does their test and then suddenly moves; you no longer have any contact information for that patient, you're sitting there with a result of squamous cell carcinoma and you can't figure out a way to reach that patient, what do you do with that? That's a major problem.

So, that potentially -- obviously presents patient care issues, and potentially liability issues, because you -- could the lab be sued for failing to report a result because they couldn't find anybody to report it to.

How are the results reported now? So, you can mail it to the patient, assuming that their address is still correct. If you mail it to the patient, you have no idea whether they received it or not, so if you're mailing an abnormal result, how do you know the patient got it and had the potential -- the ability to act on it?

Obviously, if you call the patient you know they've received the results; you don't know if they've understood the result, and there's no permanent record for them to hold of the result.

Obviously, electronic means provide some ways -- email, for example, provides a way of getting some confirmation of receipt, as well as having a permanent record, but many patients in this 15 percent may not have access to electronic communications readily.

Then, of course, you can use multiple methodologies. You can give a phone call, followed by a mailing, potentially creating confusion when patients receive multiple different reports at different times, and making sure they understand that those are all the same report, and what to do with them.

Then follow up results. How do patients without a doctor follow up with on abnormal results?

So that, again, is the -- another crux of the issue, is that if you issue a patient a result of ASCUS, or a result of LSIL, and they can't get to a doctor to have the next step in management done, then you really haven't done them any good. So I think that's going to be an import issue to address, as well.

So, in conclusion, self-collected Pap's not identical to provider collected Pap's. I think Shyam made a really good point about the FDA having approved ThinPrep and SurePath as a system, and I think this is really -- it's not

fundamentally a minor modification of the existing system; it's a fundamentally brand new system that we're talking about here, and so we need to evaluate it as a brand new system, and evaluate the entire system as a whole.

So, there are a wide range of issues that are distinct from provider collected Pap's; collection and transport issues, choice of lab issues, lab interpretation issues, reporting issues, follow up of results issues.

And there's a distinct potential for patient harm; there are quite easily ways to see more women being subject to harm by a test that’s not as sensitive as the current Pap test, then women being helped by a test because they aren't currently being Pap tested.

So, there's a real potential for patient harm if it's not thoroughly demonstrated to have identical performance to provider collected Pap tests.

That's my last slide. Thank you.

MR. KALAVAR: Thank you, Dr. Staats.

So, our next speaker is Dr. Schiffman. He's a Senior Investigator with NCI.

DR. SCHIFFMAN: Hi. You're going to see a lot of unanimity here, so I'm not going to repeat the overlap, I'm just going to say a few extra things and then we get to our talking.

I see that attempt to focus down on just getting cervical cells from a self-collection to be difficult because we're trying to simplify, unify, and get to a point where we have a new simple public health message for preventing cervical cancer deaths, and reducing morbidity, so it's really hard to not broaden the discussion.

So, I'm going to give general background, and I see it as a broad comparison, and very difficult to just lock down to that one question.

Okay. So, that's the CIL statement. We do a lot of work -- I've been working on this for 35 years, on cervical cancer, and HPV, and that's all I've done. So I've worked with a lot of companies doing NCI independent research, but sometimes the different companies, for both cytology and HPV,

have given us test reagents at no cost. I have no financial conflict of interest.

So, there's a central background. The one thing is the cervix is not a point, and it's not a field; a cervix really has typology, and it has typography, it is distinct. The lesions are distinct, on the same cervix, around the T-zone, even. Even around the transformation zone, you can find a CIN-1, a CIN-2, a CIN-3, and normal, and with very distinct points.

Now, this is related to where HPV is found, and not found, and where there's cervical abnormalities, and not, and this is from real micro dissection studies in which we, micro dissect tissue and look at both the histology and the HPV, and whatever. Very intensive studies.

And so, there is no such thing exactly as a field that can just be sampled broadly, even though cytology is a exfoliative technique.

So, when you talk about a cervical versus a

vaginal specimen, it's impossible, because they're opposed, it's a potential space, and there is exfoliation that occurs naturally.

So there is some cervical material in vaginal collected pool, and there is -- the feeling still is that the techniques are best when you scrap directly, or somehow other sample, the lesions themselves, and that you cannot, in fact, count on just a general measurement.

But there is, also, no clear division such that you can just talk about a cervical collection because there -- that -- of course, this is just the potential space, and there's a back and forth, in terms of where the cells are found.

But the purpose of cervical screening is to reduce cervical cancer death and suffering by detection and treatment of cervical cancer precursors. What we call pre-cancers, and we're getting away from all the different terms, and also to avoid doing harm to women, especially those not truly needing treatment.

So we don't want to catch a lot of people who have false positive results, in terms of being at risk. And the chance, in the United States, or in any place, of somebody dying from cervical cancer is a few percent in high risk places, and it goes down with our good programs, to 0.6 percent, cumulative lifetime.

So, a lot of what we do in screening is really on people who, even in a place like Malawi, which has really high incidence that's seven percent cumulative incident. So, 93 percent of the people would never be helped by a program.

So you have to be really careful in public health to do right, and do a very focused effort, so that we don't do 20 exams over a lifetime that are not helping many people.

I also wanted to, in terms of basic facts, to bring up again this idea of the increasing importance in the United States of adenocarcinoma. We've controlled squamous cell carcinoma much better, but an important fraction of cervical cancers are adeno now, and both are caused mainly

by HPV, but the same pathway that we talk about all the time for cervix cancer, is not known nearly as well, in terms of pre-cancer, the adenocarcinoma-in-situ for adeno.

And in Kaiser, which has a very good program, it's up to 35 percent are now -- or even 40 percent are adenos.

And we still see a very different ratio of adeno in-situ, which is the target. Something -- you're trying to prevent cancer. Adeno in-situ is only about 1.5 to 1, where's 10 to 1 still for CIN-3, CIN-2, 3, to squamous.

So, when we talk about what are we trying to Hit, we're trying to hit a treatable precursor lesion that can be by treating, prevent the cervical cancer from occurring, and -- or at the worst, a very, very early cervical cancer that can be treated to affect mortality.

So, we understand the pathogenesis of squamous lesions much better, but we always have to be concerned, do we have enough adenos and adeno in-situ in our studies to make conclusions about

whether a technique is going to work?

Now, all of our guidelines, and we're involved in all of these guidelines at NCI since 2002, with different organizations, are working on the basis of absolute risk from cohort studies and trials. We don't just use relative risk, or just do small studies; we're doing our conclusions based on very large follow up studies that actually measure whether risk is being reduced by a technique.

So, I can say right away, is my conclusion, that we just don't know the answer to this question. We can conclude right now in saying that in the PubMed literature there is not a contemporary study to address the question posed in this symposium.

So, Dotty is going to give us informationshe's really done some sleuthing to go back to some work that was done on vaginal, which contains some cervical cells, and whatever, but that stuff -- when I started in the field in 1980 that was already accepted, those thing were known from a previous

generation of Papanicolaou students, and I think you're going to say that we found some of those, but this is pre PubMed, so if you really want to talk about a contemporary liquid based cytology, and whatever, just not there.

So, we're going to have to do new studies if we want, and they have to be big if they're going to meet contemporary standards of evidence, and we don't have those.

I'm going to not go over what we already -- you've seen these, so I'm not going to go over them again. I'm going to just mention, again, that we're moving towards this era of vaccination and screening together for control, and you have to be considering the vaccine effect.

So, when we talk about 21 to 24 year olds, a lot of them are now going to start being people in the partial vaccinated with some kind of herd protection community.

So, even though there's guidelines starting at age 21 now, even in the Preventative Services Task Force, we're going to be changing the 21 to 24 pretty soon,

because those people are going to be decreasingly helped by cytology, as we know it, or even any kind of screening.

So, there's going to need to be changes, and we have to bring in the context of a vaccine and what it's going to do to guidelines going forward, and techniques going forward.

Again, I’m not going to repeat -- I'm just going to say -- also, another major modifier that continually gets us is what to do for post-menopause when the T-zone is even farther into the canal, and so -- and treatment is even more difficult, because it's hard to do colposcopy when you can't visualize the actual lesion, and surgery itself can be more morbid. It's a more uncomfortable examination. The downsides of screening are hard.

So, everything has to have some kind of affect modification, in both the younger, like the 21 to 24 year olds, and also post menopausal women. We

do have to consider age when we're making recommendation for any test, or device, or technique.

So, we're really talking about screening. This is, again, was just said. And then triage of screen positive women so that we don't over-treat, because not everybody who screens positive, it needs to be treated, and we're talking about cytology, and we're not talking about HPV, but I don't see we can not talk about both of them, but I will restrict to cytology.

Even cytology needs to be triaged because the most common cytologic abnormality is equivocal. Meaning, it's bigger in category than all the others combined, so the most common non-normal cytology is we don't know if this is abnormal.

So, that has to be really considered that cytology needs to be triaged. In that case, it's being triaged mainly by HPV testing.

And I'm not going to talk about low resource settings, except that I do want to say that for

low resource settings within the United States, when we came and talked about self-sampling some years ago, NCI FDA conference, we were told the FDA doesn't usually have special population recommends. They don't usually say that we're approving this but only for, you know, the Appalachia, or for boarder places in Texas, along the border, or something.

So, we have to have a general good rule, even though the needs may be quite different in the different areas.

So, we're asking will self-sampling work for screening, or will it have a role for triage? And we're restricting our self to cytology based, but cytology based doesn't always mean just the Pap smear.

There are cytologic methods now that aren't a conventional -- and this is where it gets into research, so I'm saying that these are not approved uses yet, so I'm going to just mention that as we're talking about this new method, that there may be new kinds of cytology that are

associated with it that are not, in any way, to be considered approved uses yet.

The devices, as we talked about, I think the devices have not shown themselves to be that different, one from the other. Even from the most simple cone brush, all the way to the more complicated and expensive ones. That it's not the device so much, but there's a lot to do with the issue how do you transport, and all the other things that we just mentioned.

So, the conclusion, of course, is that cytology -- we don't have information on how to do this, or if cytology -- if you're going to be able to get cervical cells, to begin with, off a self-sample reliably.

We are, with Phil Castle, and Megan Clark, and some others, looking about how often even clinicians fail to get a good cervical specimen, and revisiting the issue of adequacy.

Because with our Kaiser colleagues, we're finding, as we review the few cancer cases that do occur, we're finding that

inadequacy does figure into a fraction of those, maybe 15 percent, or higher, and that for example, in the obese women, it's very difficult sometimes to visualize because of redundant vaginal folds, and opposed vaginal folds, that if you don't have an extra large Graves speculum, and if you don't use the condom method, you may not get a really good cervical specimen from the T-zone. You might not be able to see on colposcopy if you do have a lesion.

So, the notion that even clinicians have trouble with the right tools, getting a good specimen, makes it hard for me to visualize how we can guarantee that a self-sample would always hit the Os and get a targeted specimen.

I want to bring that up because we're studying that directly now.

I’m not going to mention HPV because I was told not to.

And just that the triage for cytology has been HPV ASCUS, and that is the most common non-normal finding, and we have guidelines for how

to do this.

But there are these novel methods, and I'm going to mention them, and immediately say that these are research. I'm talking about research now. That there's automated cytology that might help increase the reliability, reproducibility, and sensitivity of whatever cytology we do.

There's also dual stain, which is coming forward, and it might be that you get enough dual stain positive cells that are found, so that it works. But these are coming forward, so I'm not going to spend a lot of time on those.

And I'm not going to talk about the molecular visual, just to stay to the out of scope I don't even know if it's allowed to present some of the research findings, but basically, these are promising techniques.

Without any kind of endorsement, I'm just saying that they're -- the human, or the cytotechnolgy, red, is going to be supplemented, or even replaced, by automated cytology, and/or dual stain, and I leave these slides in the pack

for people to look, and call if they want to talk about them offline.

And the molecular techniques are working very well, as well, but we're not talking about those.

So, I'll repeat the issue about adenocarcinoma. We know for sure that cytology is not as sensitive a screen for adenocarcinoma in-situ, as it is for the squamous precursors, and we know for a fact, that there are molecular markers that are working much more sensitively than cytology, particular for adeno, and we lack evidence on the relative sensitivity of self-sampling for these cases that are higher in the canal. But they have to be considered as increasingly important in the United States.

So, in summary, a personal opinion, I'm skeptical. I'm skeptical about a self-sampling strategy that's going to be able to hit the Os and get the lesion, so that we have representative cells, even for adenocarcinoma precursors.

I am hopeful about research uses for molecular

tests, where you have a lot of ability to find stray molecules and have positive signals, and we have some evidence that those might work.

But I remain to discuss how that would be, but it would be a totally new, to me, device and needing to do a substantial study to prove its worth, relative to other options that we have for preventing cervical cancer.

MR. KALAVAR: Thank you, Dr. Schiffman.

So, our presentations for the morning is over. The next item on the agenda is panel discussion. It's supposed to start at 10:40, so what we can do is take a quick break.

The break is not originally included in the agenda, but since we have a few minutes a five minute break and then we'll come back here at 10:40, and in the mean time we'll get set up for the panel discussion.

(A break was taken.)

MR. KALAVAR: Okay. So we have the panel discussion members all seated. Most of the panel

members you have been introduced to. There are two that were not speakers. Dr. Cunkelman and Tamika Felder, so I'll give an opportunity to -- and Dr. Rosenthal -- I couldn't see you, you were hidden back there. Yes.

Dr. Rosenthal, Dr. Cunkelman, and Tamika Felder, so I'll give you three an opportunity to introduce yourselves. Please go ahead.

DR. ROSENTHAL: Figure out how to use my equipment. I'm Dotty Rosenthal. I am emerita -- they've now changed it from emeritus for, you know, gender reasons, the emerita at Johns Hopkins University. I was the Director of Cytopathology there, and so I've devoted my whole career to cytopath.

I'm delighted to be here, and I'll talk a little bit about the history of self-collected Pap's before PubMed.

DR. CUNKELMAN: I'm Jackie Cunkelman. I'm an OB/GYN and urogynecologist at the FDA. I am also still in clinical practice. I'm over in the Office of Device Evaluation.

MS. FELDER: My name is Tamika Felder. I'm a 16 year cervical cancer survivor, diagnosed when I was 25 years old, was treated at Johns Hopkins. Thank you for the wonderful care. I had a radical hysterectomy, followed by chemotherapy and radiation, and I am now a patient advocate.

I started telling my story, and I went in to find other women to connect with to get them talking, so that we could, you know, get rid of this stupid stigma that prevents people from getting screened, getting vaccinated, from sharing their story, which just hurts the cause overall. So I started an organization called Cervivor, spelled C-E-R-V-I-V-O-R.

MR. KALAVAR: Okay. Very good. So just note, we're going to ask questions, the FDA will start off with some questions, the audience is welcome to ask questions as well.

So, for the panel members, please state your name before you answer the questions for transcription purposes. Okay?

So, let me begin with a question. I want to

go over some of the numbers that Dr. Saraiya put up in her slide. 12,000 women develop and 4,000 women die of cervical cancer each year. In 2012, 8 million U.S. women, ages 21 to 65 were not screened for cervical cancer in the last five years.

So the question is, what is the reason for this many women not getting screened? Is it due to gaps in cervical cancer screening, and if it is, what are the gaps? Now, this is a question to the panel as a general, and you guys can try to answer it. Who wants to go first?

MS. FELDER: Okay. As someone who did not get screened, so I had a couple of reasons for not going in and getting, at the time, it was yearly, my yearly screening, and it was because I had graduated from college, I moved to the Washington, D.C. area to be a television producer, which is what I always wanted to do, and I had a wonderful career, but it was a career of freelance and there weren't health benefits.

At 25 I didn't care about that, I just wanted

the job, and you know, you think you're invincible, you don't get sick, or anything like that.

When I did get health insurance, I went to a doctor, a new doctor here, and the doctor was unkind to me. The doctor said that, oh, your belly is so big, if you were pregnant you wouldn’t even know, and different things like that, and it got the best of me emotionally and I didn't go back, and I should have gotten screened.

I used to blame myself, but a wonderful doctor by the name of Dr. Philip Castle reminded me that it's not my fault.

But I want to make sure that other women don't fall between the cracks. In my decade plus year of doing this work, over a decade now, what I've learned from women is that there are various reasons why they don't get screened.

When I was looking at the list above, I thought all of those things are true; being in a rural area, you know, people having body image issues.

People think that it's too big, we have to do something in this country where busy career people, whether you have a family or not, you can't take off from work.

I love my doctor. I finally found one that I loved, and she caught my cancer. But I had to spend three hours in there every time I went, and I would have to leave D.C. go to Maryland, come back, and for women it's not fun going back to work somewhere after you've had a Pap smear. Even if they give you a wet one, or whatever, you know? It's not fun. I'm just keeping it real with you.

The other issues that I don't think a lot of people talk about, and it may be a small percentage, but I've seen it multiple times in the organizations and the women that I support, that there are women who are also physically abused, and they do not want to go and get screened because they're battered and abused, and those are things that we also have to think about when we think why women are not going in and getting screened.

MR. KALAVAR: Any other comments from the panel members?

DR. SARAIYA: Yes. When we examined those 8 million women -- Mona Saraiya. When we examined those 8 million women, and why they weren't getting screened, we actually did a breakdown, in terms of whether they had a doctor's visit in the last few years, whether they had insurance, and it was really surprising to see at least half of them had insurance, or had seen a doctor in the past three years.

So I think it's an opportunity we have to think about, that this opportunistic screening environment that we have, not everybody has a reminder and recall system for reminding patients to come back for a screen, and many times it's highly dependent if their insurance is changing, so they're in a new insurance system.

So, there's a lot of disconnection between the systems. So those are a few things, in addition to mentioning some of the social cultural issues that have already been raised.

MR. KALAVAR: Go ahead, Dr. Rosenthal.

DR. ROSENTHAL: I agree with everything that's been said, either from the stage or in this conversation, but I also would like to refer you to two very interesting recent websites. One is MMWR, which recently had a study in which they compared incidences and death rates of cancers in rural, suburban, and metropolitan areas, and I won't go through all the data for you, but as you can imagine, the rural areas had higher death rates, although, lower incidences, and I guess it's lifestyle and non-processed, non-fast foods.

Then part of it referred me to the CDC. I went on for cervical cancer specifically, and they had the states broken down by death rates from a whole variety of cancers, including the cervix, and as we have discussed, it's the south, including Texas, and some of other areas in the Rust Belt, that have the highest incidences, and it's because of lack of access.

And now that -- I hate to be political, but I am, because I'm a political person -- with Medicaid

access, or Medicaid funds being threatened, then you're going to have less and less access, and these women can't go miles, and miles, and miles to the nearest clinic.

They also have, as Tamika mentioned, they have all kind of job, healthcare -- I'm sorry -- childcare issues that just keep them (from) going, and as we all know, the precursor lesions that Mark talked about, which is our target, those are silent.

Until a lesion becomes invasive, and really, it's after it's minimally invasive, does it ever become symptomatic, and by that time, as you know, the cat's out of the bag.

So, it's access -- to me, access is the most critical part, and self testing may come into play there, but with all the issues that Mark Schiffman brought up, I'm also skeptical.

Later on, if we want to, I can talk about the pre-PubMed studies that were done very, very briefly.

MR. KALAVAR: Thank you. So, based on what

I'm hearing, you guys have identified certain issues, certain factors, that are affecting access to healthcare. So, how does self-sampling address those issues?

DR. STAATS: Paul Staats. Well, I think I addressed this in my talk already, but certainly, if you look at access as being the number one thing, then potentially, if you have direct marketing to patients of device that's relatively inexpensively priced, you potentially have women who are getting access to that, who wouldn't be able to afford or have access to going into see a physician.

So, there would be potential benefit to that group in that way. Obviously, if you look at, you know, experiences of not having a good experience at the physician's office, or just generally having a fear of physicians, or personal, or religious beliefs, against certain aspects of the medical experience, then you would, potentially, have those women also gain access to this device.

So, I mean, I think, really, if you look up

and down the list of -- you know, again, just convenience and, you know, just the barriers of getting to a clinic, the barriers of work, of childcare, etcetera, all of things, potentially, are all mitigated by this device.

So there -- I think almost every category you can think of, there's the potential for this device to reach some of those women.

I think the challenge, as I laid out in my talk, on the opposite side, are actually getting to these women. Getting them to know about the device, getting them to get access to the device, is it priced at a point where you can get it, and then, you know, on the follow up, if and when one gets an abnormal test, being able to do something about that test. Those are the challenges.

And so I think there's a balance there. There certainly is the potential for reaching some of these patients, maybe many of these patients.

But there also is a lot of difficulty in challenges in reaching these patients, and that's why they remain unreached.

DR. CASTLE: (Off microphone.)

MR. KALAVAR: It could be confused with self-collection for HPV.

DR. CASTLE: (Off microphone.)

MR. KALAVAR: So I think when you talk about self-collection, I think there are lessons we can learn from self-collection from the research that's -- or the work that's been done for self-collection for HPV testing, from a programmatic aspect, which we'll discuss in the afternoon.

But I take your point, yeah.

DR. STAATS: Paul Staats, again. I was just going to say, in response to that, that my understanding is that we have limited this discussion to self-collection for Pap testing, and that for my part, whenever I use the word self-collection, I am referring to self-collection for Pap testing in the context of this conversation.

DR. ROSENTHAL: Me also.

DR. SCHIFFMAN: Just the notion of self-collection, I was able to see a direct to consumer video, and an advertising campaign, that

I found, regardless of how it's being tested, to be elegant, and very attractive.

I, of course, am the worst person to ask whether it would be effective, but it was emphasizing the privacy, the self-empowerment, and the tool itself was elegant, and it was done very well.

So, to have the ally of, like, very well done direct to consumer, would be welcome, in the sense of getting participation from some people who might not want to come into a clinic.

MR. KALAVAR: Okay. So we have -- I think Phil also had a question, and then we have Dr. Cornelison. she's a gynecologic oncologist from CDRH, so I'll let her ask her question.

DR. CORNELISON: Well, hello. Good morning. I’m Terri Cornelison, and it is so wonderful to see so many of my colleagues here, so welcome.

I wanted to ask a question to, sort of, hone this discussion a little more towards practicality. Your moderator asked the question, what are the barriers to screening, and that's

sort of very broad, but what I really want to know, is I want to hone that in, because we really want to address those intersection points where upon intervening we can make a difference.

So, women who are unscreened, who upon knowing that they have a cervical cytologic abnormality, would overcome those barriers to seek treatment for that; is there a population where this type of intervention, that those women would welcome it, and ask upon it, and you would close a gap of an unscreened population.

Such as yourself if, before having insurance coverage, and in your very busy life, if you had -- if there was a way for you to have known that there was a cervical abnormality, would you have overcome the barriers that you had for accessing care, to access care, and therefore, getting a better answer, and perhaps a plan for you? Thank you.

MS. FELDER: Thanks for the question. Tamika Felder here. At 25, I don't know, but 42, obviously now, knowing all that I know, and doing

the work that I do, absolutely.

I think, when I talk to women, there's still a lot of women who, especially if they go to a free screening event and there is some type of abnormality found, a lot of times they don't know where to go, how to get follow up. You know, we try to make sure that if we're working with someone to do a free screen event, that it's also a screen and treat event, and there's some type of follow up care for them.

But, I would hope that, yeah, I would follow up and do what I needed to do, but as a young woman I just -- at that time, thinking of my mindset, I don't know. I was just so scared by what happened to me, in general. But all I can do is try to help women, going further, as we move.

DR. SARAIYA: Mona Saraiya. I do think that, you know, there's certain populations that if they have insurance, and they may not be used to the whole screening component; I'm speaking specifically to some foreign-born populations, immigrant populations, that are not used to the

concept of coming in when you're well.

So that particular group, I believe, if they had the system in place, they would be able to -- they would follow up, knowing that they have the ability to follow up. Because they just don't -- they just aren't used to the concept of screening, so that's one group.

There's several other groups, I think, like that where it's an inconvenience. So they may have the insurance, but it's an inconvenience for them to be screened because they're past the reproductive health age, where they're seeing the clinician on a regular basis, that if they were -- you know, or had the ability to screen, or self-collect, and had an abnormal result, they would follow up.

MR. KALAVAR: Okay. We'll let Dr. Castle ask his question.

DR. CASTLE: So, I have two questions. The first question is a clinical specific question, which is given that these under -- and this is really focused on under and unscreened populations, what parameters, from a screening

standpoint, would you emphasize? You know, is it sensitivity, specificity?

Again, these are under and unscreened populations, who are also more likely to be lost to follow up. So, what protocol would you actually use?

And the second question is, what is the -- in the view of the panel, what is the standard of care for cervical cancer screening globally?

DR. SARAIYA: Taking your last question first -- this is Mona Saraiya -- well, the World Health Organization has come out with cervical cancer screening guidelines, and surprisingly so, for the first time, in 2014-15, they're promoting HPV based screening.

What they actually say is that they have an algorithm that says is your Pap test -- if you have a cytology program, they ask you specifically, system and quality indicators, in terms of coverage and follow up, and they actually say if you haven't started a screening program yet, do not pursue a cytology based screening

program.

So, most of the country, other countries, are thinking about HPV based screening. Even Latin American countries that were traditionally very resistant to HPV based screening, are actually thinking in that direction.

In terms of the second question that you asked, I'm sure I can address all of it, but I would think that one test for women who are rarely and never screened is that you want to get them the best test possible, and knowing that they might not be coming in for another routine screening test. So highly sensitive, as well as specific.

DR. ROSENTHAL: Dotty Rosenthal. Phil, thank you so much for raising those questions. I was in South Africa the mid to late 80s, I can't remember exactly. I had the opportunity to speak with the Minister of Health. I was working in one of the hospitals, in fact the hospital in Soweto, which has a very, very high incidences of cervical cancer, which is why I was there, and there really

was not an organized screening program.

So, I went in, I was young, and I was brash, and I said to the Mister of Health, why don't you have a screening program? And he took a deep breath, and he looked at me, and he said, you know, he said, we do have opportunistic screening; when a woman comes in for something else, we will do a Pap, but he said, if we screen the population that really needs it, we wouldn’t have the clinicians, the adequate number of clinicians, to take care of these women.

And that really made me think about access, and that's why, you know, I keep emphasizing it. You have to do something with these abnormal tests.

Now, women go into denial; there's no question about that. But most of the time they've been scared by some incident, and now, through public education, hopefully they're not as scared as they used to be, but it's still -- it's a real access -- what happens after the abnormal Pap?

DR. CASTLE: This is Phil Castle, again. Let

me ask the question in a different way, and it's going to be leading, so I apologize for that.

Wouldn't you, in a high-risk population, who is also at high risk for not getting follow up, would you not emphasize the most sensitive protocol, which means the most sensitive test, and the most sensitive follow up?

So, you know, for example -- I won't touch the first one because you know what my opinion is about the first one, but the second one is, would you even triage a positive, or would you send them to colpo, given that, A, you want the maximum sensitivity, because you may never screen them again, and a triage negative needs some sort of follow up, which you may not get in that population.

So, in the case, regardless of what your front-end screen is, wouldn't you just send women to colposcopy to maximize the sensitivity, given that you may never see them again?

DR. SARAIYA: Yeah, and that goes back to your other leading question about WHO. I mean, I

didn't mention the treatment, but if you're HPV positive, they're recommending cryo immediately. So I think in the -- not here, in the U.S., but in the -- in the U.S., I think treatment, or you know, colposcopy is a very appropriate strategy.

DR. STAATS: Paul Staats. I mean, I think one needs to take various considerations into account, not purely maximizing your initial sensitivity, and your initial aggressiveness toward a positive. I think, you know, one wants to take age into account.

For example, in a 21 year old who's HPV positive, going straight to a colposcopy, or a leap, might be pretty aggressive, and potentially might scare women who otherwise might now enter the -- again, this is very speculative, but scare women who might otherwise enter into routine screening, to say that, wow, that was really (simultaneous speaking) --

DR. CASTLE: Well, let me qualify; I wouldn’t screen anybody under 30. I wouldn’t screen anybody under 30, so let me just qualify.

DR. STAATS: Okay. Well, that's -- I mean, that's not what the current guidelines are.

DR. CASTLE: I understand, but this is public health. This is about unscreened -- the cancer rates are extremely low in under 30. I realize that, from a society standpoint, we're still uncomfortable with that, but really, the key population, what WHO recommends, what we recommend, let's say, if we were using HPV testing -- again, we don't use HPV testing -- well, 25 and up, so it wouldn't be, and -- so what I'm really talking about is getting one or two screens in high risk populations who, essentially, 25 or 30 and above.

DR. STAATS: I mean, arguably, if you want to absolutely maximize sensitivity in a group of unscreened women, you would co-test them.

DR. CASTLE: Yes, if you could get cervical samples that were qualified, and you're really talking about 5%.

DR. STAATS: (Simultaneous speaking) --

DR. CASTLE: And you're really talking about

five percent -- you're talking about five Percent.

DR. STAATS: What is the most sensitive approach to unscreened women, - my answer, what's the most sensitive approach for unscreened women, would be co-testing. If -- again, we're having a discussion about what it would take to get (simultaneous speaking) --

DR. CASTLE: But the starting point is cytology here, not --

DR. STAATS: -- adequately sensitive and similar to cytology. That's sort of the point of what this -- we're actually, honestly, a little off topic here, I think, because we're talking about self-collection for Pap test, not what would be the best method for women to (simultaneous speaking) --

DR. CASTLE: But it does -- but it does color what the conclusions are, in terms of making --

DR. STAATS: (Simultaneous speaking) --

DR. CASTLE: Let me finish. In terms of making a recommendation of self-collection in Pap, if it is less than the standard of care, then we

should not be offering the less than the standard of care to anybody in this country, or anybody in the world, in my opinion, and if we know that they're at high risk of being loss to follow up, which this population is, that we're talking about, the notion of standard algorithms, where let's say, just for the sake of argument, we screen them with HPV and we're going to do cytology, no, you wouldn’t do that in a high risk -- I mean, just fundamentally from a clinical epidemiologic standpoint, you would maximize -- because again, you want to find as much disease in that one interaction as possible.

I'm not saying you're treating CIN-1, I'm saying you're treating at the threshold that's acceptable in the United States, but understanding the parameters by which you're dealing with a special population, you would want to frontend maximize the performance of your screening algorithm for this special population.

DR. STAATS: Paul Staats, again. I agree with that statement, that you would want to maximize

your sensitivity for this screening population, absolutely.

And I do think, in the broader scheme of things, it would be preferable to look at self-collection as a whole, and to look at performance of self-collection as a whole, and if somebody wants to try to bring to market a combined HPV Pap self-test, then one would look at that unit as a whole, compared to current standard of care, as opposed to looking at the individual Pap test.

But when we're looking at, specifically, somebody trying to bring to market a self-collection device for Pap testing, to me it would be fair to compare that to provider collected Pap testing.

And that should be the basis for comparison, is can we demonstrate that that device performs as well.

And then separately, we would look at management guidelines, to groups that do management guidelines, would look at management guidelines for self-collection. But to me, this

discussion is about self-collection devices for Pap test, and how one would look at what the FDA would want to bring that to market.

DR. CASTLE: (Off microphone.)

DR. STAATS: Fair enough.

MR. KALAVAR: Go ahead, Dr. Crothers.

DR. CROTHERS: Barbara Crothers. I am representing the American Society of Cytopathology, and I'd like to echo Dr. Staats' comments about self-collection as a whole.

I think, Dr. Castle, you were saying that no One is disputing that self-collection has value; I think that is the discussion, and even though we're trying to limit it to Pap testing, at this point, we can't talk about this without talking about HPV.

There are some serious lab concerns, that I think Dr. Staats brought up already, when you're dealing with mailed samples, and the reporting, and everything, that apply whether you're doing Pap testing or HPV testing, and as has been pointed out already, the FDA needs to look at the

system as a whole.

So, I do think this discussion is relevant to both, even though we are discussing its feasibility for cytology at this meeting, I think it does have value that we have this discussion, and carry it over to HPV testing, which holds a lot of promise.

So, I don't think we want to take those things off the table, but we have to be realistic about the challenges we're facing, from a laboratory point of view, those are very serious when you're talking about self-collection, compared to what the current standard is. Thank you.

DR. FOURNIER: Good morning. My name is Dr. Art Fournier. I'm a Professor Emeritus of Family Medicine at the Miller School of Medicine in Miami. Also, a grandfather of self-sampling, trying to use it in underserved communities in Miami for 35 years, and in Haiti for the last 20 years.

I'm currently working, actually, to try and help get a national cervical cancer program going

in Haiti, and we've had some data, and actually, it's relevant to the discussion we just had.

The standard of care that's been adopted in Haiti, based on World Health Organization, is screening using self-sampling and community health workers as para-educators and para-facilitators of that, followed by acid wash and treating the positive acid washes with cryotherapy.

The advantage of that is it cuts down the number of women who have to get into stirrups by 80 percent, so that radically reduces the amount of people that you have to have, examining rooms, doctors, etcetera, etcetera.

What should be done next? There's still some controversy, and we'll probably be bringing forward several pilot projects to see what the best strategy from thereon is.

But I think the value of self-sampling has been demonstrated in the international arena, and that value in the international arena applies for our underserved communities here in the United States equally as well.

And the other thing is, I actually believe that we should look at self-sampling -- excuse me -- HPV testing cytology, and testing for STI's, all as complimentary tests.

If you can get them all from one sample, give the clinician the maximum amount of information they need, and lower the total risk for it, not just cervical cancer, but for tubal ovarian abscess, ectopic pregnancy, and HIV infection.

DR. ROSENTHAL: Dotty Rosenthal. When you are collecting the sample, and you have a caseworker going out, I assume, someplace either nearby the patient, or even to the patient's home, what do you do for the cytology exam? Who reads them? How long does it take? You know, all of these issues that we've already discussed.

Because in certain areas, the numbers of people who can read Pap's is very small.

DR. FORNIER: That's true. Right now, as I said, we're using HPV testing. I'm doing a pilot study; we did our first 85 patients last June. The good news is that the specimens stayed out in

the Haitian heat for over a month before we get them to the United States; we have a laboratory in North Carolina that did the specimens.

The cytology didn't look that good, so for now, we're going to stick with the HPV testing.

Partners in Health is sending their pathology to the Brigman Women's, they are celebrating that they can get the results back in six weeks now. I'm not sure that that's quite the solution.

It's work in progress. We're working on it. We're plugging away.

DR. ZARITSKY: Hi. I'm Luna Zaritsky. I'm a reviewer her at FDA, and my question is, mostly about follow up and making sure that the women who do get those abnormal results are actually, you know, going to see the clinicians.

So, in your opinion, with whom does the responsibility lie to make sure that these women actually take that next step and see someone? Should it just be up to the patient; you get your result, it's up to go? Should the manufacturer be responsible for providing some sort of, you know,

some resources, maybe in the labeling, or phone numbers?

I know tele-medicine is something that's been kind of thrown around. So what are your thoughts on that?

DR. ROSENTHAL: Dotty Rosenthal, again. I will, I promise, not talk so much.

If you use Cologuard, which is advertised all over television, as a predicate system, that's by prescription. Physician has to write the prescription in order for the patient to get this -- the test, and then they send it in to wherever the lab is, and the results go back to the physician.

If we're doing self-testing -- let's just talk about the cytology for right now, and it goes out to a woman in Texas. Texas is a big state, and the number of clinics for the underserved is very small. She may not be able to go, even if she gets an abnormal result, and if she knows the significance of the abnormal result, she may not be able to get to a clinic, for obvious reasons.

So, what does she do with that? It's also a matter of patient education. She may not know what it means; atypical squamous cells of undetermined significance? Half of our colleagues don't know what to do with that either, which is why we have wonderful HPV testing.

So, there are a whole lot of factors, and I think your question is right on. You have a huge amount of socioeconomic issues, socio-educational issues.

The American Cancer Society used to say, give yourself a birthday present, get a Pap, but that information has to get to the women who are the least likely to get it, and the most needed to do screening.

So, thank you for the question; I don't have an answer.

DR. SARAIYA: Mona Saraiya. In our breast and cervical cancer screening program we spend 40 to 50 percent of our funds to follow up women. So, I think this reaches underserved women, but only ten percent of the eligible population, based on

current funding, but I can't emphasize enough how important the system are that are in place, the reminder recall system.

So you can take it outside of the individual provider system, and obviously, those women who are under screened, under served, are going to be going to family planning clinics, community healthcare centers, and you know, whether that's through the breast and cervical cancer screening program, or not.

I also wanted to just raise, specifically, we oversee the Pacific Islands where, you know, there might be an island of 50,000 women only, and they have several outer islands. I can't emphasize enough, after 10 to 15 years of supporting that program, we still only have 20 to 30 percent coverage. And having gone to visit the island, a visit -- at least one of the islands, it was amazing to see what kind of barriers there are.

So, not only -- there may be one provider on the main island, and a nurse practitioner, or a healthcare worker, they're very resistant to

seeing somebody that they know, the family knows, even for cervical cancer screening.

So, I think that there's some areas, one, that's so geographically disbursed, such as the U.S. Pacific Islands, that may benefit from self-collection strategy.

DR. CASTLE: This is Phil Castle, again. Mark, given your -- and again, you're not -- I mean, you're not representing the FDA here, but could you talk a little bit about what a trial design would be to validate self-collection and cytology, so we have a sense of the magnitude of the kind of validation that would be necessary for this -- you know, putting my own skepticism aside, you know, at the end of the day it's about data, so --

MR. KALAVAR: Some -- you know, validation, I think that's the topic of the afternoon. Would -- maybe we can --

DR. SCHIFFMAN: (Off microphone.)

MR. KALAVAR: Sure. Sure. Again, the afternoon session is completely devoted to

validation, but (simultaneous speaking) --

DR. SCHIFFMAN: I can start now and talk into the afternoon.

MR. KALAVAR: No -- please, go ahead.

DR. SCHIFFMAN: Just very simply, we are now in a -- we have -- we are counting on big prospective, count them up, studies. They are not relative risk studies, odds/ratio studies, association studies.

They would have to be a full out proof of efficacy, and that means a minimum of tens of thousands of people done in such a way that you have enough outcomes, and so you're looking at a PMA for something like this, and this is -- there's enough questions raised that it would have to be a very large, tens of millions of dollars study.

DR. CASTLE: (Off Microphone.)

DR. SCHIFFMAN: Yes. So there's no simple way to answer this question, because we don't have any data.

MR. KALAVAR: So, as a reminder, please speak

into your microphones.

So, go ahead, Dr. Crothers, after you, I think I'll switch gears and talk about a different topic. Go ahead.

DR. CROTHERS: Okay. Barbra Crothers, and this question is actually -- is for Dr. Cunkelman. Because I'm -- I would like to hear the concerns of the gynecologic community about self-collection devices.

DR. CUNKELMAN: So, speaking for the entire gynecologic community, you know, I think a lot of the concerns of the gynecologic community are the same things that have been brought up by other panelists, in terms of having a test that is reliable.

The thing that comes to mind most for me is what some of the other panelists have brought up, which is just -- is not just that patients are under screened, but once they're screened -- that's one piece of it -- once they have an abnormal, I think a lot of people don't know where to go.

And I've seen patients who -- when I was even practicing in euro gynecology, I was still doing some general gyn at that point, and doing colposcopies, and I'd have people come to me who had been looking for a doctor for months, and they knew they had an abnormal test, and these were insured women, and still not being able to find somebody to follow up with.

So, when I look at this problem, I think screening is one piece of it, but I think that -- you know, there's a much bigger issue.

One of the other things that I've brought up, and I think one of the other people asked this question, in terms of follow up with patients and relaying abnormal cytology, within the gynecologic community the gynecologist who collected that sample is responsible for following up with the patient, and that's not just a simple phone call or a letter.

When you have a concerning result, and you attempt to reach a patient, and you don't get a response from her, you have to keep trying and

documenting, because in our medical legal environment in the United States, that is fodder for legal action.

So a patient cannot follow up on a result, even if they were told the result, and ultimately the clinician can be held liable. And I think that is also something that has to be taken into account.

I don't have an answer to that, but if this is shifted to patients, sort of, directing their own screening, and then it's up to the pathologist to relay that result to them, and really get them in with adequate follow up, that could be problematic.

I see a potential role for it, if it's physician directed, if we have an adequate test. I think when it goes to, sort of, over the counter patient directed screening, it -- there are a lot of moving pieces that need to be taken into account. It's not as simple as just providing Pap smears and then cervical cancer will be eliminated.

MR. KALAVAR: Okay. I'll let you go.

MR. BOYLE: Thanks. Sean Boyle from Roche. I thought it was really interesting that the fecal occult blood test was brought up, and I'm curious to know, and this is probably not the best panel to ask, but you may know, are there findings from the implementation of that, that we could benefit from looking at it, in terms of many of the concerns that have been expressed by the panel and others?

DR. ROSENTHAL: I didn't look at the results. I looked at the overall implementation of the test. I wanted to find out how it got to the patient. You know, they advertise it on television, ask your doctor if this is right for you, and then the patient does have to take the initiative, or maybe the physician is saying, you're high risk, let's do this.

But it is physician ordered, and that's what I was looking for. I didn't go into, you know, what the pick up rate was.

DR. SARAIYA: This is Mona Saraiya. CDC also

supports a colorectal cancer screening program, but it's a little bit different, in that states are allowed to administer whatever screening test they want.

Just looking, briefly, at the literature, and there's been many systematic literature looking at mailed kits, as well as pre-addressed labels, they do significantly improve coverage for FOBT and follow colonoscopy.

And I must say that many of the organized screening systems here in the United States, like the Kaisers, etcetera, have implemented those and have been very successful increasing coverage.

MR. KALAVAR: Okay. So we have about 20 minutes remaining, so I want to cover a very important topic before we run out of time. I'll give you a chance to ask a question; if you will just hold off for just a couple of minutes. Thank you.

So I want to switch gears, and maybe talk about some safety issues. So considering we don't have a lot of knowledge about the collection

devices themselves, when you talk about self-collection from the cervix, do you see any safety issues? Patient safety issues? Patient injury? And so on?

Maybe we can start with Dr. Cunkelman.

DR. CUNKELMAN: So I know you and I have discussed this before. You know, obviously, if the device itself had sharp edges, or something like that, there's a potential for harm.

In general, my concerns with self-collection aren't really related to the safety of placing something in the vagina, per say, in terms of grossly -- I mean, patients place tampons, they place medications.

Assuming that the device itself doesn't have qualities to it that would make it inherently harmful, the simple act of placing something in the vagina is not my biggest concern with self-collection. I have a lot of concerns with it; that isn't the primary one.

MR. KALAVAR: Okay.

DR. SCHIFFMAN: Mainly we talk about drinking

in the buffer. Having a child drink the buffer. That's --

MR. KALAVAR: Yeah, that was my next point. I think Dr. Staats sort of covered this in his talk, the collection media. So if it's part of the collection kit, and it's -- self-collection is taking place at home, there's potential problems associated with the media. So that's another consideration.

DR. CASTLE: This is Phil Castle. We were so worried about this we used mouthwash in our study in Mississippi. Could we just -- I literally woke up one night, was sweating, going we can't send preservative into the homes, we have no way of regulating it, and one child drinks that, any good that we've done with our -- you know, pilot study, done. (Simultaneous speaking) --

MR. KALAVAR: So your specimen collection media was mouthwash? Dr. Castle, I just want to clarify you said -- did you say mouthwash?

DR. CASTLE: Yes.

DR. CUNKELMAN: I would clarify, too, that my comments were just related to the actual device. People have asked me several times, well, should women be placing things in their vaginas, and quite frankly, women place a lot of things in their vaginas, and that's no problematic.

So, I share your concerns regarding the fixative. I was just referring to the actual device, and should women put things in there.

DR. STAATS: Paul Staats. And again, the primary fixative, I think, is about 30-40 percent, by volume, of the ThinPrep preservative solution, which is the most common liquid based testing, is methanol, which is -- can cause blindness and fatality, so it certainly is a concern.

And if one comes up with an alternative preservation medium, that is considered safe, then one is dealing with an entirely different test, which needs an entirely different, potentially, set of diagnostic criteria.

You know, if you look at conventional preparations versus ThinPrep and SurePath

preparations, pathologist and cytotechnologists who screen liquid based preparations, need to be specifically trained in analyzing those specific preparation types.

You can't, just because you -- because you've done cytotechnology school, or you've done a residency, you can't just go out and do liquid based screening right now.

So, if you come up with a different medium, you're coming up with a different test that potentially needs a whole different set of training and criteria for diagnosis, and so that's not a minor issue, if you change the buffer.

DR. CROTHERS: Barbara Crothers. Dr. Staats, could you address some of the patient safety issues concerning patient identification linked with the specimen?

MR. BAILEY: Paul Staats, again. That's a very good point, Barb.

So, when a physician, or a provider, collects a specimen they write out a requisition, and they put a patient name and identification on it, when

-- they also label the container.

If patients send something that's inadequately labeled, there would need to be careful criteria to make sure those specimens are rejected up front.

Potentially, again, where we don't have a provider to provide reports to, getting those reports back to the correct patient, are potentially, obviously problematic, in terms of the patient getting the report, but also in terms of people who shouldn't be seeing that report getting access to it.

If you send a report by mail, you know, we talked about domestic abuse survivors, you know, if a spouse, or someone in the family, who doesn't approve of this testing gets the result, that's potentially problematic.

It's also potentially -- there are potential HIPAA violation issues for the lab, by providing that information by mail, or potentially somebody who shouldn't be seeing the result is opening it up.

Then, obviously, you know, just making sure that the name, the address, of -- the date of birth, all those things are all consistently reported by the patient collecting the results, is going to be critical to actually getting the right results to the right patient.

So, you know, having -- giving a result to the wrong name, but that goes to a doctor who knows that's not one of their patients, is one of the additional checks on making sure that the results are going to the right patient, and that's lost if you're directly sending it to a patient with the same name.

MR. KALAVAR: Go ahead.

DR. ROSENTHAL: Dotty Rosenthal. As I mentioned, I went back to pre-Pub literature, and I'm going to refer you, in the interest of time, I'm sure -- those of you who really are working with cytopathology know the name Leopold Koss. He's an absolute -- was an incredible historian, as well as a wonderful cytopathologist, surgical pathologist.

If you go to page 223 in the Fifth Edition, there is one column devoted to self-administered sampling. He began this in the 1950s, along with a colleague -- actually Papanicolaou and a colleague, began looking at tampons to collect samples, vaginal samples, and they were successful.

What they did -- this was in the clinic, and I'm using this example as something to think about, as a perhaps preparation issue.

They took a tampon that was ingeniously designed and it was put into the patient's vagina, and left for varying amounts of time. They studied how long it should stay in. They took it out -- this was in clinics, of course -- they took it out and then at the end of the tampon that would proximal to the cervix, they stamped it on a slide.

Now, the old -- and they got a very nice cell sample.

Now, of course, this was fixed immediately. If you go back into the literature, or if you were

trained in the old days and I was, these, of course, were conventional smears, and one of the fixatives was hairspray.

I mean -- Phil is shaking his head -- and it didn't give the most wonderful fixation, but it was good, and you can use -- I mean, the labs would send out hairspray.

You also can use 70 percent ethanol, which doesn't have the methanol in it, it gives very nice cell fixation, but here, again, the criteria are a bit different, so there's training involved for the labs.

But all these things can be overcome, looked into. I think, really, instead of taking the time here today, just making the device manufacturers aware that we have all of these concerns, and they're going to have to iron those out.

But the main thing is, I think, the sensitivity and specificity of however we collect the cell sample is the most critical issue.

MR. KALAVAR: Thank you. So we had a question back there? So, after your question, I just want

to remind Dr. Staats, you have a question from online; maybe you can cover that after the question here. So --

MS. KLEIN: My name is Elizabeth Klein. I'm the CEO of GyneConcepts. We are the company that are currently in the FDA with the self-administered Pap smear device.

Is that better? That is the first time in my life I've been told that you couldn't hear my mouth. So, thank you, that was a compliment.

I can just tell you that in the last two hours I cannot even imagine how my head is spinning. First of all, my pay grade doesn't allow me to be here because you're all very bright. You have all different ways that you're coming at what we've asked for.

I would just like to see us concentrate on the fact; do we have worth in self-collection?

We don't need to get into the needs today. There's a lot of issues that you, as clinicians, and doctors, need to get on your own and figure out.

You know, the FDA is only going to look at a device, and before they look at our device, we've already had to prove to you that it's ISO approved, and everything you've already wanted is clean and clear. It could never be inserted in a woman's vagina, and have anything wrong with it, no sharp edges. It's all been tested.

It's gone through, you know, drop tests, it's gone through the tear test, it's gone through the sensitivity, it's gone through injecting -- crushing it and injecting it into pigs. All of those things are done before it ever gets to you.

So, when it finally gets here, we're only asking, from the private sector, is to give it an opportunity.

You talk about the women you're not reaching; well, you're not going to reach them until you allow yourself to open up to something different. We've asked, through the FDA, and we will be a physician's approved, once we get to that point; it's not going over the counter. Those things happen way down the road.

The physician has to use it, has to be assured of it, has to make sure of how they will use it.

I currently am a Kaiser member. I get 90 percent of my healthcare through the mail from Kaiser. I do my work at home, and when I go in, I see a physician for ten minutes and he reads all my charts that this came back, this came back, your stool sample looks great; I mailed all that back in, nobody had an issue with any of that. It's all labeled, it's all done, now it's an app on my phone. Our device will be an app on a phone, if they can use phones.

But the idea behind this device was never to come in to United States of America and take people away from their physician. The women that want to go to the doctor are going to go. Those that can't afford to go, we need to help them find a way to, at least, know that there is an avenue and a place to go.

I, too, have had bad experiences. The reason my husband, who is here, designed the Pap smear and is our inventor, is because of the

unbelievable Pap smear that I had, and I came home and said -- we have 12 children, if you want your wife alive, and you don't want to have to take care of 12 kids, you better get on the drawing board, because I am not going back, and I didn't, and I've been self-testing for now 11 years, and I do fine, and I've picked up an STD, and I've picked up -- I've picked up a bunch of stuff.

This device works. It's not about my personal opinion. It's that we want you to understand that our goal with the FDA, and for the American people, is to help save lives. It's to give people opportunities to do better. To come in.

There are ways to get around all the things you've talked about today. Every one of you have a different position, and all of your positions are so valid, so we're not even trying to approach that subject.

And to you, Dr. Rosenthal, I met with Motumbo in the Congo, and he would show me where they would have 10,000 women with babies on their shoulders walked up in the heat and stand out for

days to get a Pap smear.

So, what we said to him is let's get you a portable lab, let's get a mobile lab over here, and we can get that done, and we'll give you these devices.

And so, instead of you seeing that one doctor to see 25 women in a day, your clinician can do 30 and 50 women in a group, show them how to use it, and then you run your test on your lab.

At the end of the day we found that he needed less than seven percent of the people to come in, and actually see a doctor. But they had to have the test.

So, these -- this is value, and its value, not only for our country, it's worldwide, and this is really what, humanitarian, we should be looking at.

So, I don't look at anything then -- I've used it, my grandchildren use these things, we've all been self-testing for a long time, just to make sure we're comfortable.

It is a convenience factor, it is a financial

factor, it is a frightening factor for many women, I hope that some of that can be put aside because doctors are busy, they can't always -- when you go in, you lose half a day of work. We know that. It's hard. Daycare is hard. So, all of those factors figure in.

But let's just open our minds today, and think about is self-collection valuable? Does it have a place in our medical community? And I happen to personally think it does. Thank you very much.

MR. KALAVAR: Thank you, Ms. Klein.

So, you're welcome to respond and also, I'd like that question answered, and then we have several waiting here.

DR. STAATS: If I may start by addressing that? I don't -- my impression, listening to these talks, and to this panel, has not been that anyone has pre-judged for or against the concept of self-collection of Pap tests, nor has anyone evaluated at all any specific device, and so I don't think anything that has been portrayed so far should be a reflection on any specific advice.

I think our task here, and what we've tried to lay out here, are what we, from various perspectives, see as potential problems that need to be addressed, and what the FDA is asking is what needs to be addressed? I think that's all that has been discussed here.

I would say that rather than say that there is a device that may benefit some patients, and therefore should be FDA approved, that what we should really be looking at, in terms of a public health and screening, sort of circumstance, is overall benefit, in terms of cervical cancer, and if one can bring a self-collection device that is equally sensitive, and specific, and performs equivalently to the Pap test, then that device may very well have a role in cervical cancer screening.

Given that 85 percent of women are currently screened approximately according to guidelines, we need to balance very carefully any potential harms to women who are currently screened, versus the potential benefits to women who are not currently

screened.

So, I think it is very much -- should very much be within the FDA's purview to look at the overall societal impact, not just is it beneficial to one patient, and I think that's an important part of this.

So, should I now turn -- should let other people (simultaneous speaking) --

MR. KALAVAR: Yeah, we have about five minutes remaining, so if you can --

DR. STAATS: Sure. So, I've got this question handed to me on an index card, which I'll read to you (simultaneous speaking) --

MS. KLEIN: Can I respond (simultaneous speaking) --

DR. STAATS: You don't want this?

MR. KALAVAR: No -- no, go ahead. You can go ahead. We only have five minutes, Mr. Klein, we can -- we're going to have an additional afternoon session, can you hold off on your questions for afternoon? We only have five minutes, and then we have -- we'd like to give the others an

opportunity to ask questions as well. Thank you.

DR. STAATS: Okay. So, quickly, "One fact you did not address in your access to care assumptions was in your discussion the percentage of uninsured women, was that once the woman receives an abnormal Pap result, in many states only then does she meet eligibility criteria for cervical and breast cancer program, thus, the biggest cost barrier for uninsured patients is actually the initial access to Pap. Currently that cost includes a physician fee and lab fee. Can you speak to whether you believe that factor would impact your calculations?"

So, certainly that would, on the margin, impact the calculations. I don't know the details of each individual state's, or in general, the existing treatment programs.

But certainly, I think, in general, getting a Pap result in women who otherwise are not, will raise their level of -- getting an abnormal result will raise their level of concern, generally, to the point where it may overcome many of the

existing barriers.

I think, potentially, this is a -- that particular situation is one where the barrier may be lowered slightly. There may be a little bit more availability of medical care, in some circumstances, but I think that's marginal and not going to markedly change my overall point that just getting an abnormal pap result is not enough, that there will remain many barriers among the unscreened population to actually getting appropriate treatment for an abnormal result.

DR. ANDREWS: Jeff Andrews. I'm an OB/GYN. My question is to any panelist who'd like to respond.

I see a parallel between cervical cancer screening and breast cancer screening, and the FDA website says that a woman does not require a prescription, or an order, or a referral for a mammogram, but can self-refer, and I'm wondering if you see a possible parallel there?

DR. ROSENTHAL: I don't know the answer to that, from a standpoint of self-referral. But if

a woman has the ability to be referred -- to self-refer to a mammography unit, then she has access.

The next question is, where are the results going to be sent? And perhaps the mammography unit can say, okay, here -- you know, we can give you five physicians who will follow you up, and I think the same thing applies to Pap.

It's the cost also. I mean, the cost of mammography is considerably more than the cost of a Pap.

So, if that's any kind of an answer for you, I'm -- some states do have self-referral, and some don't, and some insurance companies -- you know, etcetera, etcetera.

DR. ANDREWS: Thank you.

MR. KLEIN: I think Betty, or my wife, said a lot more than I -- or covered a lot of the topics that I was going to mention.

But I have to think, and I am the inventor of the device, and we have found that there is a very, very positive attitude with women.

They feel more empowered, like Ms. Felder over

there, about taking care of their own healthcare, they're motivated to take care, and just like Dr. Rosenthal said, people are -- even down in the Congo, and places like that, we met with the basketball player who has developed a clinic specifically for taking care of women's healthcare needs.

I think with -- not being critical, but I think I hear more negativity coming back as to reasons why it can't be done, as opposed to why it can be done.

Dr. Staats, I mean, I've listened to your reasons, and they just go on and on to the point where you say will a person put the sample in the envelop and mail it off to the lab to get the test results, and then if that -- and what happens if it doesn't get mailed back? I mean, it's just a literary of reasons why it won't work, and I think you've got to put -- get a different mindset about it.

We tested women, and they came back -- I posted -- interviewed every woman we tested, and

each woman that we tested -- I got 50 percent of the women that volunteered to talk about something that personal, said this is incredible. This is the most easy to use device I've ever seen. It took me three minutes, I was in and out, I was done, it was that easy. Why it isn't in the marketplace now?

We had, believe it or not, in our testing, except for three patients, 100 percent effect results. 100 percent.

The three that didn't work were, one, she had just started her period, literally before she came that afternoon, but still came in for the test, and of course the cell sample was not satisfactory for the computer to analyze.

The other woman had had a hysterectomy, and for reasons she didn't tell us, so we couldn’t get a cell sample. And the last person, or volunteer that came in -- but the third person that came in she didn't seal the bottle, the cap tightly, and the cell sample was lost.

But 100 percent of the patients that came, the

volunteers, we got adequate, and as you all know, the lab determines whether or not the cell sample is adequate, not the doctor.

Our device that we have is a collection device. A doctor in Houston tested our device doing his cell samples, conducting the -- because the doctor had never done it before -- he used our device, and then used his own traditional method, and ours produced the same results as doing it conventionally.

Interestingly enough, he said this is so simple, I don't know why it hasn't been introduced a long time ago.

I don't -- I think that there needs to be more of a flexible attitude coming from, maybe, the medical community, as to, yes, there is a way to make this so people, or patients, prospective patients, can get themselves tested.

Our device, including the test, all results from door to door, or from front to back, everything, this device that we have can be on -- for the doctor, or for the patient, rather, costs

less than forty dollars, including the test, everything.

MR. KALAVAR: Okay. Mr. Klein, we're out of time, but what we'll do, is we'll have the panel respond, and then we'll make your question the last question. Go ahead.

DR. SCHIFFMAN: What I said to you in private, and I'll say again, for -- I've been doing this for 35 years with the same objectives you have, and all I'm saying is I've been mislead when we've done studies of a couple hundred people.

You know, this is -- screening is a function of millions of people in the United States, and the untoward events, and whatever, can be rare, as is the condition that we're trying to prevent.

So, I don't know -- your perfect performance is always a flag to me that maybe you haven't done thousands, and thousands, and thousands, because nothing I've ever seen is perfect when you extend it into the thousands, and then we start to see the rare but important downside.

So, all I was saying is, be prepared for the

same level of scrutiny that are we are subjecting all of the things in this class of agents for cervical cancer prevention, and I was suggesting not to talk anecdote, but that this is a large-scale issue that's going to require rigorous examination. That's all I was saying. Not negative, but realistic.

DR. STAATS: Paul Staats. I'd like to follow up on that.

I think, obviously, it's your job as the inventor to be really excited about what you have, and that's great, and I sincerely hope that you have a device that can actually meet all of the concerns that I and others have raised here, but our goal, as panelist here, is to make sure that all of the potential concerns from all the different angles have been brought up, so that the FDA can consider what it needs to address when it brings a device to market and that, perhaps, is why you're perceiving this as negativity, but our job is to make sure that patients and the public are protected and that we, therefore, do

everything we need to make sure that any device that's brought to market is well tested and well demonstrated to be at least equivalent to current standards of care.

I had one other point to make, but I don't remember it, so I'll stop there.

MR. KALAVAR: Okay. So, we'll --

DR. ALAGIA: I'll be very brief --

DR. STAATS: Sir, can I -- the one thing that I wanted to -- it's more of a question, which we don't have time to answer here, but I'm curious how your pathologists interpreted adequacy, because when I look at a Pap I cannot tell the difference between a cervical squamous cell and vaginal squamous cell.

And so unless I see endocervical cells on that slide, I would have no idea whether the cervix was actually sampled, and so I don't know how -- but given current Bethesda criteria, it would be appropriate, on physician collected samples, to call a specimen with only squamous cells adequate.

So, if you pathologist is calling those

adequate, that then I would not -- that alone would give me no confidence that there's actually sampling of the transformation zone.

DR. ALAGIA: Okay. Thank you very much. This is a great panel, and I appreciate you all pulling this together. My name is Pat Alagia. I'm a former practicing gynecologist here in the McLean area, and then went to work for a health system that took care of a lot of patients in Appalachia. I'm now working for a diagnostic company, Quest Diagnostics.

My question is this, you know, having worked, you know, where access isn't an issue in McLean Virginia, you know, northern Virginia. You know, people are asking about, you know, kind of their R&A subtype, they come with their ASCUS diagrams, whatever, great. You know, and then you work in Appalachia and they don't see people.

So, my question is, is it a matter of getting -- the first question is, is it a matter of getting a better test, or better access?

You know, and I ask that because, you know,

when we look at the 12,000 people who are diagnosed with cancer every year, you see that 4,000 are dying, and I think, Dr. Saraiya, you said that -- I think that you said that 50 percent of the patients, or maybe -- who have cervical cancer haven't been seen in the last, you know, five years.

So, the question is, of the people who are dying, are they dying having been screened, or having had access, or are they dying because they haven't had access at all?

So, again, is it a question of a better test, or access? Thank you.

DR. SARAIYA: Yes. The data -- this is Mona Saraiya. The data that was mentioned was about cervical cancer cases, not necessarily deaths, but new cases of cervical cancer and where they're occurring, and 60 percent are thought to occur among women who've never or rarely been screened. So, that's an access issue.

I think the point about the better test is a valid one. I think -- you know, we do need a test

that can make sure -- you know, if we're only going to get to a woman once in her lifetime, or less than that, how do we give her the best test possible, and you know, take into account age, etcetera, so we don't have to worry about her getting screened. So we immediately act on that positive test, and that's where there's debate about whether it's a better test.

I just wanted to also comment a little bit about where we're seeing the evolution of self-collection worldwide, especially in high resource countries. It's not occurring -- it's occurring 20, to 30, to 40 years after a cervical cancer program has been in place, so their rates for cervical cancer are not going down, so they're moving to alternative strategies, like self-collection.

And I believe in European countries, at least, where it's -- if an -- the equivalent of an FDA approved test has been approved for X or Y reason, they're not necessarily seeking approval for self-collection. They see that as a strategy.

So, I just wanted, again, raise the issue that we have 12,000 cancers that are occurring. This is, you know, several decades of screening being in place, so I do think we need to come up with a strategy, and I see self-collection as a strategy.

But we do have to take into account that these women are ones that haven't been screened, so they're not in the system, or they're in a system where there hasn't been enough follow through.

So, something has to be done, similar to what we're hearing about in Kaiser's. Like, even in the Kaiser systems, there are women who are not being adequately screened, but there is a good system in place to make sure that they have an adequate follow up, so perhaps, things like self-collection can be introduced in that kind of system, because there are women who are not being screened there, as well.

MR. KALAVAR: Okay. So, if there's no further questions, or responses, we'll -- I think we'll conclude the morning session. We're -- so we'll break for lunch. 1:00 o'clock.

(A lunch break was taken.)

DR. CUI: Good afternoon, everyone. Okay. Let's get started. I think we had really wonderful discussions and also talks, in the morning.

For the afternoon session, we are going to talk about the validation considerations for the clinical studies, if you are going to look at the self-collection devices for Pap test.

So, we are going to have two talks, one from Phil Castle, and the other one is from Marina, and Phil Castle is going to talk about HPV testing.

But I think what we are going to anticipate, it's not about the testing, it's about the way to outreach to the patient population, and Marina is going to talk about the practical considerations for evaluating these devices.

So, I just want to give a brief introduction for Phil Castle.

Dr. Phil Castle is a professor in the Department of Epidemiology and Population Health at Albert Einstein College of Medicine, New York.

Dr. Castle is a member of the Board of Directors of the American Society for Colposcopy and Cervical Pathology.

So, with that, Dr. Castle.

DR. CASTLE: Good afternoon. I am not talking about HPV testing, per my host. What I am talking about is self-collection as an outreach intervention.

So, what works, what doesn't work, in terms of getting women to participate in screening.

That's not me -- none of that's me -- well, something else will get loaded here.

So, really, there's sort of three flavors of these outreach studies, and many of them have been done in Europe, and really targeting unscreened women.

So, with many of the European systems they have organized screening, and they really know who's coming in and who's not coming in, and then they have done randomized clinical trials offering women Pap testing, like a new invitation letter, versus self-collection.

These are my disclosures. I worked with many of the companies to validate, independently validate, their technologies.

So, I want to -- today's talk, I want to talk about a systematic review of meta analysis of participating self-collection verse clinic based screening, and the systemic review of community based outreach using self-collection.

And, just to acknowledge that this is work that was sponsored by the CDC.

So, in set of studies here; this is a meta analysis of participation statistics, and let me explain what these terms mean. So, mail to all is an opt out.

So in other words, everybody gets either an invitation letter, or a self-collection kit, and they either return it -- either they come to the clinic or they return the self-collection kit.

The opt in is you actually have to go and request the self-collection kit, or another visit.

And the community campaign is much for of a, sort of, outreach at the boots on the ground

approach, where you actually, like, knock doors and engage people.

The protocol versus intention to treat. So, really that has to do with the self-collection part of this.

So, if a woman is offered self-collection, but she doesn't self-collect, but she decided now to come to the clinic, that's part of the ITT, and in a way, you know, it doesn't really matter, as long as she gets screened.

So, you have a per protocol, and ITT, we can look -- and there's not a big difference.

But, essentially, what you see is that when you -- let's see if I can see this -- so when you opt out, right? So, everybody gets something and then it's a question of whether you participate, you increase, between a new invitation and self-collection by about 7.8 percent. If you look at the ITT, it's a little bit higher.

So, some women get the self-collection kit, they decide not to use it, but they do come to the clinic.

If you require them to call up ask for it, given that these women aren't already participating, they don't do it. Okay? It just doesn't happen.

And the community outreach approach, if you start knocking on doors, of course you really increase your participation, even among the control group. But you get a big jump if you offer self-collection of about 40 percent.

And these are just, sort of, the scatter of the data, and you can see that it's a fairly consistent story, in terms of this is the per protocol, you get just a little bit higher participation with the ITT analysis, and here's your participation in the control arm.

And this is the mailed in or -- I mean, mailed out, this is the opt out approach.

If you look by difference by study, you can see that it's -- and this must be the -- well, this is the -- this must be the opt in part of this, so there's almost no difference when you just -- when women have to call to get their kit,

it doesn't -- they just don't do it.

If you -- again, this goes back to the opt out -- if you allow them to just use the kit, if you just send it to them, and if they return it, it's about a ten percent.

But there's some scatter. Some populations were more responsive than other populations here, but the overall effect is about a ten percent increase in participation.

And, keep in mind, there's no phone calls, or -- you know, these are, like, you just send the kit. Right? You identify them as non-participants in screening, and you're just sending the kit.

So, sort of the lowest level of effective intervention here is sending the kit, allowing them to do it.

Obviously, very cost efficient; you're not spending a lot of money, you're just sticking it in the mail, and you get a ten percent bump in participation.

The other question, of course, and an

unsatisfactory sample here, just to clarify, is really related to HPV testing, because the vast majority of the studies have been done with HPV testing, and so just that one caveat.

So, for HPV testing the unsat rate was one percent.

And these are just some of the diagnostic yields of offering self-collection, in terms of how many additional pre-cancers you find per 1,000.

So, of the invited, which includes both the participants and the non-participants, it's a 2.5 percent, and for the those that actually participated, it's a fairly large yield.

The opt out, and this is for the ITT, because if they come in for screening, that's just as good as if they use the self-collection -- we don't care, we just want them to get screened -- increases the absolute participation by 12 percent.

Opt in does not increase participation, and I think -- you know, people may continue to do those

studies, or have those study arms in their trials, but I think it's pretty clear by now that, you know, asking them to take on additional step in this process, of actually calling up and saying, can you send me the kit? It's not going to happen.

Door to door increases the absolute participation by 40 percent, and obviously, requires greater resources.

I mean, you actually have to go and knock on doors and engage people, and you're -- so you're really talking about, sort of, low level intervention at ten percent, or a -- you know, sort of, very active engagement and getting 40 percent.

We did a systematic review of studies using community approach to increase screening participation. These -- this was PubMed though February 16, 2017.

All these meta analysis we did, and we also did performance, which we're not presenting here, everything was reviewed independently by two

reviewers. We had preset study criteria, and then we reviewed the list until we had consensus on which studies were included.

For this community outreach approach, ten studies were included, but the -- and they had such a variety that we couldn't really do a meta analysis. So we have three door-to-door, we have two enrollment and then randomization, three where the participants could choose their intervention, and then, sort of, other approaches.

So, in one study in a Native American population, and a Hobi population in Arizona we see that -- this was community events, door to door, they have an office of prevention, they could choose self-collection at home, versus getting services at the cancer support services; 93.2 percent of the women completed their self-collection, most, 79 percent, collected at home, compared to 21 percent who collected at the office, and it was the vast majority picked self-collection.

Studies in Haitian and Latina populations who

had no cytology in the last three years, in Miami, community health workers recruited two safety net clinics, one primarily serving Latinas, one primarily serving Haitians. Participants recruited by community health worker who spoke the native language. Choice of self-collection or discussion about Pap with a provider. 121 who chose self-collection collected samples at the clinic, 46 of the women who chose a cytology discussion had a cytology within five months.

This is work that I did with my colleagues at University of Alabama. This is 26 to 65 years old, unscreened in the last three years, community health worker recruitment, door to door.

The bottom line here is that, essentially, twice the number of women chose self-collection, and twice were more -- and they had twice as likely to complete their self-collection, compared to cytology. So it was almost a four-fold effect, in terms of completion rates.

And none of these studies -- let me clarify -- we didn't -- most of these studies have not even

really looked at colpo follow up, so that I think that there's a gap in the evidence, but it's hard to do those studies in big enough size.

Now, maybe some of the European trials have reported that, and we haven't done that analysis, but it is a sort of gap, because you're really talking about a percentage of a percentage, to study the -- how well they do follow up, so you're really getting down to small numbers.

But somebody should probably go through that literature and collect that, just so that we know from a programmatic standpoint, if they participate, what's the likelihood that they complete their care?

And we really shouldn't talk about screening without -- when we say screening, we really are -- should be talking about the whole intervention. We shouldn't even have to qualify it, because it's not screening if care is not provided.

Another study in southeast Kentucky showed another -- these are all really small studies, but 31 recruited participants enrolled and completed

their self-collection.

This is in Ontario, Canada. Another, sort of, community based outreach, you know, with a variety of methods of engagements. For the participation, 13.4 percent of the eligible women recruited chose self-collection, and 35 women completed their cytology.

So, conclusions in general, a community approach using self-collected samples increases participation.

This approach is more labor intensive. The more that you're, sort of, putting people on the ground through community health workers, the -- it's just -- and I know from our experience in Mississippi, it literally was door to door.

Now, on the other hand, what happens is when you go to door to door, and you meet with these women, they'll say, well, I don't think my sister, or my cousin, or my best friend has been screened.

So, you can get some amplification of that process, you know, if it were big enough, were you start get networks of people who don't

participate.

So, the more direct engagement results in greater participation.

The major question, is the juice worth the squeeze? Is it more cost effective to use active door to door, or passive mail to all delivery of self-collection?

Like I said, you get a significant increase in participation if you really engage people at a personal level, but that's a lot of work, and so nobody, to my knowledge, has done a cost effectiveness using these kind of data, to say is -- you know, is the greater investment for 40 percent, better than the ten percent if you just stick it in the mail.

And then the question is, for these passive approaches, and when I'm talking about passive, again, it's mailing the kits out; how can we improve participation?

So, we haven't fully utilized social media. With my colleagues in Norway, we've developed an educational app.

So I think that there are, with this new technology, and I'm not talking about the self-collection, I'm talking about the social media, how do we engage underserved populations who do often have access to Facebook, whether they have it at home, or they go to an Internet café, or whatever it might be, how do we raise awareness, and therefore increase participation, so that if we do a passive approach we get more than ten percent increase? You know, can we get 20 percent?

I mean, there's a very cheap intervention. You know, you get online; it doesn't cost anything.

So, I'll just stop there. Thank you.

DR. CUI: Thank you, Phil. Our next speaker is Dr. Marina Kondratovich.

Dr. Kondratovich is the Associate Director for Clinical Studies in the Office of In-vitro Diagnostic and Radiology Health in CDRH.

DR. KONDRATOVICH: Can you hear me? Yes? Okay.

In presentation I will speak about really study design, so before my talk we need to speak about how the test will be used in real life. But please pay attention that clinical study design can be different, how it used in the real life, so please not confuse.

We're not discussing how the test will be used, because maybe you see some very strange discussion about that I need have self-collected results, I need to have professionally collected results. Of course, again, it's not about real-life situation. It's only about how to evaluate this test.

I will discuss only three points. Of course, there are a lot of nuances in the study design, which is difficult to discuss right now, but there are really three very important points.

Intended use population, how we're planning to report back results for self-collected cervical cytology specimen, then I will speak about clinical performance study about two aspects, issue with what we can call agreement evaluation

and comparison using gold standard, and then some discussion points.

Intended use population. It's really very basic principal of the clinical study design, that subject in the clinical study, intended user of the self-collection device for the Pap test, should be representative of the United States population, with regard to age, race, levels of education.

Instruction for use should be simple, in plain language, with pictorial explanation how to use.

Cytology specimen should be self-collected at home using only instruction for use. Women should not have any verbal instruction before using this device. Once the specimen is collected, users ship the samples to designated laboratory for processing.

Immediately following self-collection, woman should answer questions about were the woman comfortable with use of this device, and whether they understood how to use the self-collection device.

Consider hypothetical study. The subject who are enrolled in the clinical study are women with self-schedule appointment to cervical cancer screening clinic.

So, this woman already participates in the cervical cancer screening program, she has self-schedule appointment, and this woman were connected that -- they were proposed to participate in the study.

Definitely women who are not responsive to the cervical cancer screening program are not included in this study. But this woman, of course, will be part of the intended use population.

So, we would like that you will -- panel discussion will discuss possible biases of this study, which includes only subject who participate in the cervical cancer screening.

Because from one point you can see that -- you know that if the woman is self-screen -- excuse me -- if the woman is participated in cervical cancer screening, maybe disease is really more difficult

to detect.

So, really, for the Pap test performance, maybe this will be more difficult population, compared to the woman who are not participating in the cervical cancer screening program. They have maybe more developed disease so really, it's not maybe so challenging population, with regard to evaluating Pap test with this particular type of a specimen.

But maybe there are some -- another issue, who know that this woman maybe young, have less education. Maybe for them it will be more difficult to understand instruction, to perform this test. We would like that will discuss this issue about possible biases.

If you think that these bias is relatively large, will the clinical study should include also women who are not responders to their regular cervical cancer screening program, and how this woman can be enrolled in the clinical study, will read -- see some very good points, how can be they enrolled. So we would like to see, maybe,

different opinions about this issue.

How to results reported for self-collected cervical cytology specimens, is also very important issue for the study design, because study size, and really value of the clinical performance, is really depend on you reported results.

Look that for the professionally collected samples. We have all these categories.

And if I consider that for scenario one, for self-collected, it will be reported all these categories, then of course, we need to evaluate correctness of each category.

If we can consider scenario two for reporting results, for example, maybe this can be reported like normal, this will be like equivocal, this will be like abnormal, and of course it's unsat. So, right now I have four categories.

Or maybe we even decided to have even three categories, like normal, abnormal, and unsat.

Of course, it's really depend how these results will be reported to physician, if the

device is by prescription, we see it being that maybe there are not a lot of value, but feel free to discuss this.

Or it will be more like device, what we can call over the counter, that woman also obtain results.

Why the study size really depends on the categories, because the more categories you reported, every category should be evaluated.

And consider a very simple case that we reported only positive, which is like abnormal, and negative is normal, approximately ten percent is abnormal, so if I have 1,000 of the women, approximately ten percent, it will be a hundred, yes? So relatively big number in order to evaluate what I need to do with some statistical estimation.

But if you (inaudible) we have all these categories, and I need to evaluate (inaudible) and I know that it's only 0.6 percent, then amount thousand I have only six. So really, I have a lot of uncertainty in statistical estimation.

So, please discuss how this Pap results can be reported, what will be next step with woman with unsat. Really very interested in this question, because published literature suggests that percent unsat can be as high as ten percent.

Of course, this paper, it's really very small number. Maybe it can be different when we can have larger study, but still we can expect that this percent of unsat can be large as when professionally collected.

Right now, let us discuss clinical performance study.

So, like usually, we have a representative subject from intended use population. This is like general segment for the clinical study.

In this study, each subject has a -- while was self-collected, and I hold this lab self-collected because we discussing only Pap test. If I'm telling self-collected, it's only about Pap test, no HPV.

So, and this slide is read in laboratory using approved imaging device.

After some period of time, we would like to know your opinion of what kind of -- this time, this woman also a vial professionally collected, physician collected, there are slides prepared from this vial, and laboratory read the slide, cytotechnologist reading the slides with approved FDA imaging device.

So, right now we see that all women in this study, and women -- we really have from four different groups. One group is -- and in my -- this slide, I will present only basic idea for the very simple reporting results, positive/negative, but of course, this idea can be really easy generalized if I hear, for example, negative, equivocal, and positive.

But let us discuss the simple case, when I have only positive and negative, and of course there's unsatisfactory.

So, I have all this subject, and all the subject divided into four groups. One group will be a subject have positive by professionally collected, and positive by self-collected.

B and C, subject who have discordant results. This subject, professionally collected, negative, but self-collected, positive. And this subject, C, professionally collected, positive, but self-collected, negative, and here is double negative.

But, usually, we can evaluate positive percent agreement. We have this number, A plus C, subject with positive, professionally collected.

What is the percent that it will be positive by self-collected? A divided by A plus C.

Negative percent agreement, it will be -- this is the number of subject who are negative by professionally collected, and this is the percent that will be also negative by self-collected.

So, we have positive percent agreement, negative percent agreement. Of course, we will look at the percent unsatisfactory by professionally collected and percent of unsatisfactory for the self-collected.

The problem with this approach, that usually this agreement is not (inaudible), because we know that Pap test has a lot of reliability, and even

if you have the same slide read by two-sided technology, you have big reliability. You cannot expect very high level of agreement, but here, there are additional factor, like validity of self-collected sample.

So, and also the published literature suggests that this agreement, especially positive percent agreement, it will be not high. It's maybe around only 80 percent.

Usually in this situation, what is fix was this problem. You need to have some gold standard, and let me explain two different schemes of how we can apply gold standard.

First scheme, which I call scheme A, gold standard, is applied to all subject, and please consider this 1,000 subject, it's not like proposed some sample size, so of course not. This is like only for sake of explanation, I take 1,000 subject, in order to (inaudible) ideal study design.

So, we have 1,000 subject and we say, then, all these subject to gold standard. Look, I have

40 subject, and this 40 subject, some where gold standard positive, 38, and two were gold standard negative. I sent 20 to the gold standard, nine were gold standard positive, eleven gold standard negative.

I sent them six gold stand positive, four gold standard negative. I sent a lot of this 930 subject to the gold standard, among them 30 were gold standard, and 900 gold standard negative.

So, I can calculate all estimate of performance using this study design, yes? Why? Because here is all subject with gold standard positive, I know total number, 83, and I can calculate what is the performance of self-collected? 38 plus 9, 47, yes? What is the sensitivity? I have all subject with gold standard positive, what is the percent? Among them it will be positive by self-collected. 38 plus 9, 47, yes? So I have this percent, 56.6.

Then I can do the same calculation for the professionally collection. So again, this is the same number 38, 6, so it will be 44, and I know

total number, I can calculate sensitivity.

(Inaudible) that of course, if I know sensitivity I can calculate ratio. I know that, and look what is going with the ratio, that in this ratio I'm using this number, this, and I'm using this, yes? 38 plus 9, divided by 83, and then 38 plus 6 divided by 83. But 83 is simplified, so I really don't need to know for the ratio this total number, 83.

The same idea for the gold standard negative. Then you can see that we can calculate specificity. Of course, we can calculate ratio specificity, we can calculate positive predictive value, negative predictive value.

Let us consider a different scheme. When gold standard is applied only to the subject, which are double positive and discordant, and I am not applying gold standard to any subject who are double negative.

Then we see that, right now, table for the gold standard positive has some results, which I don't know. Like, I know that 40, there are 38

and 2, then give me 6 and 4, 20 give 9 and 11.

So I, again, try to use this table in order to calculate my sensitivity, and I see that, no, I cannot calculate sensitivity directly, but I definitely can calculate ratio.

Sometimes this ratio, you can see different terms. Some people call this relative sensitivity. In the D (ph) we don't like to use this term, relative sensitivity, so we have sensitivity and we have ratio of sensitivity.

So, in this example, I can tell that, yes, I don't know what is the exactly in this study performance of the physician collected, but I know that self-collected is 1.07 times larger, and I can construct confidence interval.

The same for the gold standard negative. We don't know exactly what is the specificity, but I can calculate ratio of false positive rate, yes? Because I know this value, this is exactly false positive.

So, I can tell that false positive rate for self-collection -- of course, again, this is

hypothetical data -- is 2.2 times larger than for physician collected.

So, in this scheme B, it's impossible to estimate sensitivity specificity, but it's possible to evaluate ratio of sensitivity, and ratio of false positive.

Of course, I can use this scheme for risk for condition B only if I know performance of the Pap test with physician collected specimen in the intended us population, but we already know a lot of about the Pap test, maybe not exactly in the non-responders, but at least in the responders we know performance of the Pap test, which is professionally collected.

For scheme B, please discuss what is minimum and maximum timeframes between two collections that can be adequate to allow the cervix to recover from the previous sampling.

But from the other point, you see that in our statistical analysis, we would (inaudible) that this is the same Pap test, yes? So I cannot have very long period of time. But from other point, I

need to have time that cervix can recover.

Please discuss design of scheme A when you need to send all subject to gold standard, and scheme B, that when you need to send only double positive and discordant.

Let me discuss gold standard. So, for gold standard you also can have really two approaches. What I call approach one, our target condition, what we call target condition is like cervical disease, and gold standard, colposcopy and biopsy if needed.

So, in this study design it will be that every subject has result. So the Pap test was self-collected, Pap test professionally collected, and then colposcopy biopsy.

Of course, in this study design, please look that we need to have data, not only for the abnormal by professionally collected, but also, we need to have colposcopy biopsy results for the subject who are negative by professionally, but positive by self-collected.

And if I will not have this subject, all my

calculation will show that self-collected is worse, yes? Because I don't use this value, which is -- I have from this 20 subject, or if it will be only some small percentage going to the gold standard, it's also -- it will be biased estimation for self-collected.

Also, consider prevalence of cervical disease, if I use gold standard, like colposcopy, then disease defined by histology. Like, for example, CIN-2, CIN-3. So, right now, it's even (inaudible) number where I use for calculation of ratio, even smaller, and if I have this smaller number, it means that confidence interval is really very large. I have a lot of uncertainty.

So, when I try to use end point, like CIN-2 or CIN-3 by colposcopy, it's really, I need to have very big study, because even this number, 40, will be really not 40, it will be much smaller.

Let us consider approach number 2, what I call. This approach was used even for approval liquid based Pap test.

Please pay attention that liquid Pap test was

approved, not based on colposcopy biopsy. It was based on the approach, which I will describe. It's called patient cytology status. Idea was like this, that you have results for the self-collected, which are read by laboratory with, for example, imaging device.

And this slide, from self-collected vial, can be also read by education committee, with three experts.

Then we have a vial from professionally collected, and we have results from laboratory, from professionally collected vials using imaging device. Then this slide is read, education community with three experts.

Then we define in patient cytology status as worst result. For example, for this slide we have ASCUS, education committee tell an ASCUS. For this slide the education committee tell an HSIL. Then for this woman we tell and her cytology status will be worst. HSIL. Then we apply this gold standard, for example, for all positive and for discordant results.

Education committee usually very standard approach, and I only provided you slides. It's a lot of papers, how it should it work, education committee, so usually we have three experts, Pap results, but expert one, we would like to have manual read because this is like the best possible knowledge, what is going on with these two slides. We are like eliminating reliability from the laboratory cytotechnologist.

Then Pap results by expert two. If they agree, then this is results of education committee. If they not agree, then we ask third person, then we apply majority rule for these results. If happens that all three are different, then they need to discuss and we can see the consensus result.

So, discussion point, advantages and disadvantages of both approaches for the gold standard, colposcopy biopsy, or patient cytology status, taken in consideration that relevance of the target condition, cervical disease determined by colposcopy biopsy. Yes, it's very relevant,

compared to the patient's cytology status.

But look at the size of the study, even for the ratio of sensitivities, like if I have colposcopy biopsy, then it's really you need to have larger study.

In your consideration please consider that we would like to have scientifically sound data, but from other point it should be least burdensome. Please consider also possibility to have maybe some post-market data.

Because for the approval of liquid based test, it was designed proposed by the panel. I think it was something like 1992. The proposed patient cytologist status, so it was approval based on the cytologist status, and then they have post-market study, which related to colposcopy, but not even for all subject, but for more like, HSIL, LSIL .

And Dr. Cui Cheng will discuss proposal in discussion points.

DR. CUI: Thanks so much, Marina, for such a wonderful talk.

So, I know we have some after time, but just like the program going forward, so please have the panelists, I want to have the panelists come to the front table. We're going to have four panelists for this panel -- oh, some people are proposing a five-minute break. So let's have a five-minute break, and then after that we will reconvene.

(A break was taken.)

DR. CUI: All right. So, let's start the panel discussion for the afternoon session. We have four panelists for this panel, and for the person who did not speak, I will give you three to five minutes to introduce yourself, and if you want you can introduce your work as well.

So, let's stary with Dr. Conlen.

DR. CONLEN: Good afternoon. I want to thank the representatives from the FDA allowing me to come up and participate in this very important concept that needs more attention.

I promise to keep this brief, but I was asked to give an overview of my experience and studies,

which I have been performing over the past ten years on self-administered Pap smears. So, I'll make this very brief and to the point.

Approximately 10-12 years ago, we saw the need for additional access for Pap smears, so we started developing a self-administered Pap smear protocol, shall we say, and we started using it in a clinic setting in -- around Lantana, Florida, which was predominantly migrant workers with poor education, low socioeconomic, and no access.

So, they would come into the clinic once a year, and they would participate with the nurses. So we used that as our first venue, and offered all the participants $25 to participate in a self-administered Pap smear.

Okay. It went very well. It was very well received. And now these patients, most of them did not speak English. They were from Guatemala. They did not read, they did not write, so what we did is we formed two large posters and put it in the rooms and that was their instruction.

They all came out and said it was too easy,

and didn't take the money. Impressive. That easy, and didn't take the money? These are poor -- no, they wanted to help.

All right. Needless to say, we left the money for the nurses for their lunch fund.

The results were outstanding. Okay? I'll tell you why in a few minutes, but let me get through the studies.

We have endocervical cells on our samples, and I'll explain that a little bit later.

Okay. So the next study that we did, is we decided we would complicate it, so we divided up the groups -- these are all IRB, all of the paperwork and everything, and we decided that we would divide them up so that it was two weeks apart, and randomize them, whether they a Pap smear done first by a clinician, or a self-administered Pap smear.

And during this time, we got to observe why this really happens and examine how the pelvic musculature of the female allows itself to have the service approached and getting endocervical

and cervical cells.

Once again, we got endocervical cells, it was very congruent with the clinicians' Pap smear, 90 percent, and once again, all the participants said, this is very easy. I'd do this in a minute. Okay.

Well, now it's time to farm out the study to a completely independent venue. So, we incorporated the family residence program and Nellis Air Force Base out in Las Vegas, and allowed them to do to the study, allowing for 1,000 patients, and all of the specimens were going to be read by the armed forces laboratory in Texas.

Once again, endocervical cells, good results, a few unsatisfactory cells. You know, nothing's 100 percent, but still, it was very encouraging.

Their statistician, had a couple hundred samples came back and said, we're going to stop this because it's -- you know, it's a lot of revenue, and resources for us, and there's no change. These are just too consistent.

That study, as well as the other ones, we then

published last year, and it's out there to be seen. But it's very consistent.

But some of the important things that came out of this, was the patients' reaction. They found it easy, they found it accessible, and they would do it. And most importantly, they would refer it to a friend.

Now, people are people. My wife tells me to do something, yeah, okay. My friend me do something, oh, really, that's a great idea. And the same with women. We’re all like that.

To reach out and get that 15 percent that we've been talking about all day, referral from someone is happy doing this, is very important, and I wanted to bring that point up.

Now, we are in the midst of -- we just started a pilot program down in Granada through St. George's University, and we've done our first 100 there. We do plan on doing more. And once again, all of this is very consistent.

We're getting endocervical cells, we're getting the same results, the patients are saying

the same thing, and they say they're referring it to a friend, and they're all looking forward to get started doing this again with the next academic year. Okay.

So, overall, I think that answers the question can self-administered Pap smears be performed? The answer is yes. Can it be done adequately? Yes. Adequately, per the Bethesda Program, greater than five thousand cells, that protocol, and we're getting endocervical cells.

Now, I think everybody should understand that even when physicians do Pap smears, they do not get endocervical cells 100 percent. I mean, 60-70 percent, depending on who does it. Their technique; there's a lot of things that go into play, and some are just difficult.

So, nothing's 100 percent, all right? We're up there.

All right. How does it work? We've done about two thousand self Pap smears developing our protocol. Okay? And what we found is that when the female does her own Pap smear, she inserts the

speculum, because we use a speculum, and when leaning forward they do the valsalva maneuver, like when you pick up something heavy, you hold your stomach tight, and what this does, it takes the diaphragm -- and remember, the female pelvis is made up of a bowl of musculature, and it depresses. Right?

How many times have you said to somebody who says they have prolapse, you put the speculum in, you ask them to take a deep breath, and there's the cervix coming down the vaginal canal.

Same thing. It comes down to the top of the speculum, and the broom goes up and samples the endocervix and the cervical area.

Very simple. Nobody would think it would happen. I was very skeptical when we first started trying, but it does work, and that's the point that I want to make today.

It is a viable option, it is certainly needed. They talked about a lot of statistics, and what if it doesn't work? We have a model that includes oversight, and follow up, and remember the other

thing is, once you get these people in your database, you have the opportunity for education going forward. We should always remember that.

DR. CUI: Okay. Great.

DR. CONLEN: So, that's all I really have to say. Thank you for the time.

DR. CUI: Sure. Thank you so much for the remarks. Dr. Booth, can you introduce yourself?

DR. BOOTH: Certainly. My name is Christine Booth. I am an associate pathologist at the Cleveland Clinic Lerner College of Medicine, and today I'm representing the College of American Pathologists as Chair of their Cytopathology Committee there.

DR. CUI: Okay. Thank you so much.

So, I want to start with a question, as Marina mentioned, for the non-responders. We know for every study we want to include -- well, the patient so that we have less bias as possible.

So, for the non-responders, so what do you think about whether the clinical study should include possibly enough who are non-responder,

because they're so hard to each. But what's your opinion of including them in the clinical study?

DR. BOOTH: I -- this is Christine Booth. I think it is important to include non-responders because, I think, in that group you may have a higher incidence of disease, given either a lack of education or a lack of access.

So, I think it is important to recruit patients who would not be routinely screen in the clinical studies.

DR. CUI: Okay. Thanks.

DR. CONLEN: I agree, they should be included, because not only are they the high-risk group, but there you're going to find out why they don't go. Why they're not pursuing this, and you will get insight into this demographic area, and use that information so that when there is self-administered testing done, you can target them successfully.

DR. CUI: Okay. Thanks. Yeah, Phil?

DR. CASTLE: Absolutely. You know, the more that it is truly population based, and

representative, the better the study is, the more generalizable it is. I think the problem here is that they are non-participants, and I would even raise the point that, whether the metrics of sensitivity and specificity apply in such a context.

If you're trying to reach under-screened or unscreened populations, it's not sensitivity and specificity, it's diagnostic yield. How many additional pre-cancers do you find per number of women approached?

And I think what I want to emphasize is that sensitivity and specificity are not really relevant to the real world. Doctors either know that someone's positive or negative, and then we subsequently find out whether they have disease.

And, in particular, in a population that is not participating in screening, really, it's the ratio of CIN-2 plus, to whatever harms. You can use harms, you know, as a proxy. You could say positivity among women who don't have disease, revenue officer the number who would be referred

for colposcopy.

But to me, sensitivity and specificity is an artificial construct that has to do with efficacy, and this really has to do with effectiveness. How much additional disease in underserved populations you find.

And so, that would be my advice to the FDA, is to start thinking about different metrics of benefit for the population, which, you know, the FDA mandate is really the safety and health of people in the United States. I mean, that's fundamental to their mandate.

So, you know, I would say that, you know, you get -- if you get an additional 1,000 women screened, and you find another, you know, 10 or 20 CIN-2 pluses, isn't that really the metric of importance?

DR. CUI: Yeah. Thank you so much. We also welcome questions from the audience. Just keep in mind that -- keep the questions short so that we can have -- we can go over more questions.

So, just one more question for the non-

responders. So, for non-responders, these are the women who are hard to reach, so I think Dr. Castle mentioned, from his experience, how to outreach to these patients, and he also mentioned social media, that's the very, well, novel way of doing that.

But what are the -- so what do you think the best approach for how to enroll these patients into the clinical study? Just your idea, or your suggestions will be welcomed.

DR. CONLEN: Well, presently, we're working with a university out in Texas, and they have a very large outreach program, but unfortunately, they're not getting the patients in. So, there's a target area that would be excellent for a continued study.

So, they're rather frustrated that they have pooled all this money into this outreach program, but they can't get the neighborhood, and it's local. It's a local neighborhood. And we see that in the inner cities.

So, these are the areas that you could go and

approach, and you could do some door to door activity, as has been brought up several times today.

The most important thing here is that, you know, once you get these people, you capture them -- you know, everybody's got a cellphone. So that's your method of tracking them.

DR. CUI: Okay.

DR. CONLEN: Okay? That and social media. And, by the way, I mean, when I talk about this, I believe in co-testing. I believe it should be cytology and HPV testing. You're only going to get, many times, one shot at this population, and you better make it count.

DR. CUI: Thank you.

DR. BOOTH: This is Christine Booth. I think, looking at Dr. Saraiya's -- her United States map that she put up today, and where we look at where the high incidence of cervical cancer is in those locations, I think, in particular, targeting those areas and going door to door. That is, you know, an area -- we know where we can target.

And I also did want to mention that, in addition to, the College of American Pathologists does have a program through their foundation where it's a C test and treat program for cervical cancer and breast cancer screening.

And there is that program where our members and our staff at the college are contributing funds to help women get screened at the grassroots level. In the past year about -- over 700 women were screened through that program.

So, I think there are professional organizations programs, as well, that could be utilized in, perhaps, in doing some of these -- work.

DR. CUI: Okay. Great. Yes?

DR. CASTLE: Absolutely, we should target those populations, but let's be real; if we're going to scale it up, there's got to be a plan for reimbursement. I've never seen anything in this country that has worked without reimbursement, and I've given talks for 15 years about adherence to guidelines, and best practices, and none of it has

made a single bit of difference.

The only thing that seems to make a difference, after we explain the science, is whether or not something gets reimbursed.

So, and again, I'll come back to those metrics. If these are women who are not participating, and you know, a very efficacious thing that is not used by women, will have a very low diagnostic yield.

Effectiveness is really the product of efficacy times participation.

So, and that's -- really should be the metric for any sort of approval or clearance, you know, or exception, to whatever we -- you know, whatever loophole can, so that we can actually prevent disease in these special populations.

I mean, we don't necessarily need to screen people who are already being screened, and I think Mona's point is that we've sort of bottomed out, and we've gotten as far as we can go, in terms of cervical cancer burden in the United States in the general population. I mean, the curve is flat.

All right?

DR. CUI: So far.

DR. CASTLE: Right. So, if we're going to make a big dent in that curve, and 50 to 60 percent of those are un or under-screened, that's where you've got to go.

But, at the end of the day, if you don't have a plan for reimbursement -- I mean --

DR. CUI: (Simultaneous speaking) --

MR. BAILEY: -- you can do a little bit, you could do 50 or 100 through a single day of screening, but when you have 8 million people who are not being screened, that's like, you know, a drop in the bucket.

DR. CUI: Different scales of (simultaneous speaking) --

DR. CASTLE: Right. So, there has to be a plan for reimbursement, in addition to all the discussion of performance. Sorry --

DR. ROSENTHAL: Dotty Rosenthal -- that's okay, Phil. Always --

DR. CASTLE: When I say screening, I'm saying

the whole thing. There is no part.

DR. ROSENTHAL: Oh, I --

DR. CASTLE: There is not just screening. There's screening and care --

DR. ROSENTHAL: I agree, but I'm -- yeah, I'm talking about the non-responders.

DR. CASTLE: No -- no, I was responding (simultaneous speaking) --

DR. ROSENTHAL: Oh, I'm sorry. About Mona?

DR. CASTLE: -- Mona's comment. When I say screening, from henceforth, in anything I write, in anything I say, I'm talking about the whole ball of wax. Because otherwise it's not screening, period. Don't even want to discuss it. I’m talking about pay for their care, their entire care, the whole package.

DR. ROSENTHAL: Yeah. Phil, I totally agree with you, and we could do the reimbursement issue, but this is not the place for it, although, I'll join you afterwards.

The non-responders, though, I totally agree need to be included in the overall population

analysis, because these are folks, the women, that are high risk. The highest risk.

And I was in L.A. right after a major door to door was taken over, or you know done, and it was very expensive, as you well know. It was a big grant to the School of Public Health and it was very successful, but it was work intensive.

And after that was over, the women who was in charge of it, said, you know, we're doing this the wrong way, we need to go where these women are.

DR. CUI: More targeted.

DR. ROSENTHAL: And so where do they go? Grocery store? Some of them really do take their kids into the baby clinics, and they have no childcare, so you get a room with playpens, and you hand them the kit, and you do a quick education with a media, you know, a TV set, and you get them educated in a hurry, and an opportunity for them to get screened in their home, with their kit.

So, I really think this is the approach we have to use now. I mean, talk about thinking

outside box.

And we can pull those women in, but then my main concern, as you heard this morning, is what do we do with them when they have an abnormal Pap?

DR. CUI: Okay. Thank you. Okay. Sure. Yes.

DR. CONLEN: You're right. You're absolutely right. Now, when we talk about screenings it's the whole megillah . Start to finish, follow up, the whole care, and that model has to be developed.

With regards to reimbursement, we've looked into this, and we've looked into some major players -- and I'm not allowed to say anything, that's why I'm hedging, is that -- that would participate in helping to get the word out, and in their chain stores, shall we say. Okay?

So, there's a lot of large companies that are very, very interested in this program, because we all realize that the cost of taking care of invasive disease, is a lot more than the simple self-administered Pap smear, or even a leep cone

biopsy.

And, of course, the results are poor versus the leep, which you can do at lunchtime on someone.

So, yes, there is availability for financial support.

DR. CUI: Thank you. Sure. Just last question for this non-responder topic, if you want.

DR. CROTHERS: Yeah, it wasn't regarding the responders, is that all right?

DR. CUI: Yeah.

DR. CROTHERS: Barbara Crothers. And I have both a comment and a question for the panel.

My comment is, is that I think we've established that self-collection would be highly valued by women. I'm ready to go get a self-collected Pap, too.

And that's a good thing, because that is a way to gain access. But that is also the danger here, because we're talking about translating women who have already -- who are already in the system,

with physician visits, with the whole package, now opting out and selecting self-collection. That's a different system.

Regardless of what test we do, whether it's a Pap test, or HPV test, it's a whole different system, and it doesn't have the same restrictions, regulatory background, QC oversight that we have in our current system.

So, we may actually be transforming cervical cancer detection in a way that we're not expecting. Unintended consequences, essentially, by moving to that different system.

My question for the panel is, again, from a laboratory point of view, and represent laboratories, what are the issue -- so FDA approval is one hurdle, but now after that hurdle, now laboratories have to validate this test for the laboratory, and can one of you address -- maybe Dr. Booth, address some of the issues regarding lab validation of self-collected Pap tests.

DR. BOOTH: Thank you, Barbara. This is

Christine Booth.

I think an issue that I have to raise is patient identification. So, I think we need to know how the patient is going to send their self-collected Pap test in, what information they're going to provide to the laboratory, what additional things that we would need to know on the clinical side, their L&P, additional clinical data that we do, often obtained from clinician offices. Also, the positive patient identification.

So, we now two forms of identification on the sample, both the patient name and either medical record number or birth date.

So, what do we do when we don't receive that information? Do we reject the test? Do we contact the patient? So, we don't really have -- right now we reject those specimens. We may contact the physician office, and the physician office may need to come and clarify that information for us, before we're able to even excision (ph) the Pap test to the laboratory.

So, that's something that we would need to consider.

The other thing is, is there a possibility -- I'm just raising this -- in a patient who may be is a domestic violent situation, where they put their mother's name on the Pap test, and --

DR. CUI: Wrong names.

DR. BOOTH: -- and they don't identify it correctly, so that the results go to their mother and not to their significant other, and come to the mail at home. So, it's just something to consider.

Finally, the possibility of validating with interfering substances that may, when the patient is self-collecting, has there been any KY Jelly, douches, all those interfering substances? We would have to consider that in the laboratory, as well as the patient's age. Whether or not they even have a cervix. If they’ve had a hysterectomy, but still have a cervix or not.

There's a lot of additional information that we may receive from the clinician office that the

patient may not be able to give us.

And if they're pregnant, or not, those kind of additional information.

DR. CUI: Yeah. I think these are the practical hurdles we do think about when we are thinking the self-collection device.

Let's move on -- oh, sure.

DR. CASTLE: I think Christine's point is worth elaborating a little bit. I mean, essentially, here we're handing a kit and then the kit results have to plug into liquid based cytology performance.

So, yes, you can tell them not to use a vaginal jelly, or whatever, or don't douche, but they may or may not, and that's part of the real experience of it, and is likely to decrease the performance overall. And that's, in a way, how it should be done.

I mean, you can have instruction -- so, many people in this room have done self-collection studies, and you have diagrammatic, and you have step by step, you know, here's the picture, here's

the instruction, here's the picture, and you can have all the information you want about what you should and should not do.

Just like on your vitamins, or your medicines, but at the end of the day, whether they actually comply with that, that's part of the real world.

In that particular case, they're not going to be under observation of a clinician. I mean, if you're really evaluating a self-collection, you are sending the kit home unsupervised.

DR. CUI: These are -- I agree. These are the things we need to consider for self-collection devices, the samples are going to be mailed to the lab by the end patient. Marina?

DR. KONDRATOVICH: Let me clarify study design, what describe (inaudible) Philip. My understanding that you proposing study design where it will be results only for self-collected, and then for all abnormal you send to colposcopy biopsy and see what is the percent, for example, of CIN-2 or CIN-3.

What kind of issue I see with this study

design. So we don't have for this woman, professionally collected Pap test.

Of course, you will obtain some yield of CIN-2 plus, but for example, benefit risk analysis, if somebody decided to switch from professionally to the self-collected, no, we cannot evaluate because we don't have data, and can I use literature to know what is the performance in absolute values for Pap test professionally collected? There a lot of variability.

You can have sometimes sensitivity like 35, sometimes it's can be almost 90 percent, so I see some problem in this data if I will not have professionally collected Pap test for this woman.

DR. CASTLE: Well, let me respond to that, which is, again, I prefaced my comments by saying these are under screened or unscreened, so one part of that is that in a standard clinical trial design, asking them to then come to the clinic to get their professionally collected, they're going to drop out. You're going to have this huge drop out. They're not going to participate.

I mean, they haven't participated up to this point, so now you're all of a sudden in a clinical trial -- either that or you're going to have a huge bias. Right? It's not going to be representative of the underserved population.

So, the conventional trial design -- well, you have the problem that they don't participate, and if you require a clinician collected, you are essentially -- have a selection -- a huge selection bias of a subset of the underserved or the unscreened, who decide to come to the clinic. It is not representative at all.

So, I agree that you can't do this in the general population, because you're going to get a big switchover. In fact, ever woman I've ever talked to in every audience, and I've given a hundred talks, and I've asked every woman in the audience -- I'll do it here -- how many women would enjoy having a pelvic exam? How many women in this audience enjoy having a pelvic exam? Well, that goes to --

MS. FELDER: (Off Microphone.)

DR. CASTLE: Well, okay.

DR. CUI: Thank you.

DR. CASTLE: Now you've ruined my statistics. Go home.

I love Tamika, so she knows I'm just kidding.

DR. CUI: Yeah. Thank you so much. Yeah.

DR. CASTLE: So, yes, if you offer it to the general population, then you have an issue of are they getting less -- you know, lesser cancer prevention, and that is a problem.

DR. CUI: Yeah.

DR. CASTLE: I’m not referring to the general population, I'm referring to special populations whether are not being served by.

So then you move from a metric of sensitivity and specificity to diagnostic yield. How many additional pre-cancers are you finding in this, and again, you're not going to get them to do the dual sample. It's not going to happen.

They're not already -- they already not coming (simultaneous speaking) --

DR. CUI: Okay. Let's just leave these

practical issues apart --

DR. KONDRATOVICH: Yes, (simultaneous speaking) --

DR. CUI: Let's concentrate on the scientific issues here --

DR. KONDRATOVICH: Yes, and on study design because, still, we need to have colposcopy biopsy, so they still need to visit some clinic, so -- no, I don't see --

DR. CASTLE: I'm sorry, I disagree --

MS. KLEIN: Let me just --

DR. KONDRATOVICH: Okay. This is a good (simultaneous speaking) --

MS. KLIEN: I'd like to respond back to you, to Richard.

I think the one thing, because we did test in Texas. The one thing that we're finding universally near where we test, is we're forgetting about people that are illegal, and this is a large part of the population that's not served, and they don't want to come in because they don't want to give you their name, they don't

want to have all this immigration thing on them.

And we lost over 180 people in one setting because they thought that we were there for the wrong reasons. We made it clear, but I think we need to recognize there's a population out there that’s not served because of their status in this country.

DR. CUI: Thank you. Just one more for Dorothy, and then we move on to the next --

DR. ROSENTHAL: Yeah. We're talking about two different aspects of approving a device.

The FDA is concerned about safety and efficacy.

DR. CUI: That's right.

DR. ROSENTHAL: Nothing else.

DR. KONDRATOVICH: Yes.

DR. ROSENTHAL: In order to say this device is safe and effective, you've got to have a parallel trial that Marina has described.

Now, when you're -- and you're not out in the boonies yet. You have to set it up with doctors, gynecologists, in clinics and set it up so you get

the self-collected, and a short time later, as Marina described, a conventional Pap, and then you put them together, and you see how they compare with each other.

Once it's shown to be safe and effective, then you can take it out in the boonies, and then do a post-approval study to see what the yield is with colpo and biopsy, right?

DR. KONDRATOVICH: Good. Yes.

DR. CUI: That's a good point. Yes.

DR. KONDRATOVICH: For example, yes, I --

DR. CUI: The next question I have for the panel is supposed there are going to be a dual collection study design, there are going to be two collections, so what is your opinion about the minimum and maximum of the interval between these two collections? Yeah?

DR. CONLEN: Okay. So, I have done, like I said, a couple thousand, and 450 under very formal studies, and I am above 90 percent consistently all the way through.

So, statistically speaking, what is the

likelihood of the next hundred not working at all? It's low.

I know for contact lenses they do 20. I know that this is a new item, so I would say -- what I would like to see is, probably, a thousand that are consistent with what we've done presently, and then go and -- there must be a category where it's ongoing review.

Because what we don't want -- we can't lose track of, is that 4,000 that we want to go after. (Simultaneous speaking) --

DR. CUI: Yes, let's concentrate on the interval. Yeah, let me repeat the question. The question is what is the minimum and a maximum interval between these two collections, if we are going to follow the dual collection design.

DR. KONDRATOVICH: Yeah, because --

DR. CUI: Because you are going to have self-collection and professional collection.

DR. KONDRATOVICH: Yes, because --

DR. CONLEN: I have done --

DR. KONDRATOVICH: We heard, like you give

like two weeks --

DR. CONLEN: Yeah, we did two weeks, and then we've done them in the same day, and we've done them a week apart, and there was no difference --

DR. CUI: Okay. Thank you.

DR. CONLEN: -- in the quantity and the quality of the cell collection.

DR. CUI: Okay. Thank you. If you have any comments from the audience, go ahead.

DR. KONDRATOVICH: You know, like, it's interesting -- data because -- at papers, which I looked published, there were not a lot of, but -- like two weeks.

Some my colleagues who are explaining me a lot of about cytology, they have time like eight weeks, but I see that you given even one day, yes? So even like one day apart and you see that there are no problems with increase of unsatisfactory results, yes?

DR. CONLEN: The --

DR. KONDRATOVICH: Because, of course, we would like to hear if in the clinical studies that

we will not introduce additional biases.

DR. CONLEN: The question was the first pass specimen, is the first pass specimen with the broom, does it take away a majority of the cells so that you're not going to get accuracy in the second. So that's why we went back and forth.

DR. KONDRATOVICH: Yes.

DR. CONLEN: And we did not see any difference, and that was from the cytological point of view, because we were working with pathology, and they read the cells.

DR. CUI: Okay. Yeah. Please.

DR. SCHIFFMAN: Mark Schiffman. We've done a lot of same day multiple collections. Sometimes, depending on what the implements are, you can even get a sense that maybe a secondary broom is picking up things that are exfoliated from the first scrape.

I mean, it's a problem if you're then going to do some colposcopy examination, because you may have some bleeding, especially if it's a friable cervix in an inflamed kind of area.

But I don't know that it's definitive that you really get an ordering effect when you do two in a row, because the implement doesn't pick up everything it exfoliates, and you could be leaving, actually, cells behind that the second implement -- depending on what kind of implement it is -- picks up.

And I'd like to also point out that it has a lot to do with this idea of targeting the cervix. If you are, in fact, really hitting the Os right on, then it can be more interfering than the studies we've done, in which we've presumed that the self-collection cytology is missing to a more degree, therefore, less interfering with the following clinician one that's done right afterwards.

Because we're not seeing, in our minds, without the speculum, that it's hitting exactly the same place.

That's all.

DR. CONLEN: Oh, you're right. I mean, there's a lot of variation here.

DR. CUI: Can you --

DR. CONLEN: (Simultaneous speaking) perfect test. So -- for anybody, whether it's clinician, or self-administered.

DR. CUI: All right. So the next question will be about gold standard, as Marina mentioned, there are two schemes Marina mentioned, the first one is having the colposcopy and the biopsy as the gold standard, and the second one is using the cytologist status as a gold standard.

So, I want to have opinions from the panel about these two approaches, which one do you think will be more appropriate and more effective? Yeah, please.

DR. CASTLE: There should be no discussion; it's histology. I mean, that's what we make clinical decisions on, in terms of treatment.

DR. CUI: Yeah, in the --

DR. CASTLE: And that is the benchmark for all other cervical tests, liquid based cytology and HPV testing, there should be no -- if you're going require an efficacy trial, then it has to have an

efficacy endpoint.

DR. CUI: Okay. Thank you. Any other thoughts?

DR. CONLEN: I'd have to agree with that.

DR. CUI: Okay. Thanks.

DR. BOOTH: I also think that it's important to have those four quadrant biopsies as well because I think, you know, the colposcopy has to be standardized, not just a colposcopy with -- you know, I think --

DR. CASTLE: (Off microphone.)

DR. BOOTH: Right. Right. So, I think it's important that, if you're using histology, that there's standardization to the way the biopsies are obtained.

DR. CONLEN: I don't know I would -- I don't think you'd get a lot of participation with four quadrant colposcopy examination. That's a --

DR. CASTLE: There's not been an issue with that in any of the studies that have done it, and you actually look at the amount of tissue removed, if you're doing a micro biopsy you actually remove

less tissue.

Now, there's debate over whether that's the best practice or -- I think the key piece of that, in doing colposcopy, is that you don't simply look at it and say -- try to determine which is the worst looking lesion, the point is to sample all the lesions.

DR. BOOTH: Yes, because more tissue, more disease.

DR. CONLEN: Now, are we talking about abnormal?

DR. CASTLE: Yeah, these are screened positives (simultaneous speaking) --

DR. CONLEN: Okay. All right. Yes, that's fine.

DR. CUI: Okay. All right.

DR. SCHIFFMAN: This is a critical question -- this is Mark Schiffman again. I don't want to break any, you know, barrier, or anything like that, but when we're doing HPV tests, we have reference standard tests that we compare it to, but I don't understand this; you're comparing

self-collection to clinician collection cytology. You're comparing HPV self-collection to HPV clinician collection, if you eventually get to it.

I don't understand why we're compartmentalizing, in terms of design, when in fact, I do believe that what you're really asking about is the marginal increase in yield of true pre-cancer by permitting a -- or encouraging a self-sample in addition to -- for outreach, to get more yield of real pre-cancer, while not over treating.

It seems to me that we have to, as public health people, consider the reference standard is the technique that actually produces the greatest yield of pre-cancer, therefore reducing cancer.

So, this sort of siloing of reference standards make no sense to me at all. I'd like to hear why it is (simultaneous speaking) --

DR. KONDRATOVICH: Consider situations that we really need to show that device is safe and effective, and if for laboratory professional collected specimens, it was demonstrated safe and

effectiveness compared to the Pap smear, conventional, and this shows that it was larger yield of cytological abnormalities, and then data, additionally, where post-market.

It was also scientifically sound approach, and less resources for the company, and then definitely for public health.

So, maybe some question we can ask through post-market study.

DR. CASTLE: See, I don't --

DR. KONDRATOVICH: So, here it's interesting question that, yes, I understand we can require colposcopy biopsy, we have some additional concern because of self-collect that we require, of course, colposcopy biopsies really very expensive procedure compared to the cytology, and also study size definitely will be larger.

DR. SCHIFFMAN: So we're embarking on this study now -- we're doing a big study that's underway, and it will be histology is the reference standard, and it's a multi-biopsy reference standard to -- of all acetowhite

areas so that we get maximum truth, or whatever.

What I was asking was, from the public health point of view, we want to know how to introduce self-sampling in such a way to reduce additional cases of cervical cancer, and cut into the -- that suborn residual thing, and I don't understand why all you need to do is compare cytology to cytology, and -- we're embarking on a new thing, self-sampling; why wouldn't we just ask, in general, what is the best test that -- and the best approach? It's not just --

DR. KONDRATOVICH: No, I think that may be little confusion with medical practice, and how it will be used in real life. It's a lot of questions, scientific, and I don't think that the sponsor needs to answer all scientific question, or how the test will be used.

DR. CASTLE: Well, again, I will say that -- and when you say effectiveness, you're not really actually talking about effectiveness, you're talking about efficacy, and they're two very, very different things.

In a special population who doesn't participate in the program, I'm arguing, and I guess I'm disagreeing with Dotty, and I'm disagreeing with you, that efficacy is not the relevant metric anymore.

Because if you expect them to come in -- this is a population who's not coming in, so you're really not even targeting the intended use population, which is not the general population, it's the special population.

So, what I'm asking you to do is to think outside of the box, and not in a traditional clinical trial structure, which is not going to work for a population who doesn't even participate in routine screening, let along in a research study.

Now, can you imagine going to some of these populations and saying, we're going to have a special study, you haven't even participated with your local gynecologic oncologist, but we're going to bring in this team, and we're going to -- you're not going to have representation at all of

the people that you very much want to reach.

And so, I am saying, and I'm sure I'm completely out there on the diving board alone, that a standard clinical trial structure and approach for special populations who do not participate in routine screening, is the wrong design. I'll just say it; it is the wrong design, it doesn't answer the question, which should be about effectiveness, not efficacy in this particular case.

DR. CUI: Thank you.

DR. ROSENTHAL: Okay. Dotty Rosenthal. I think we're jumping ahead of ourselves by asking for a clinical trial with those patients who don't appear for screening.

We have to first show that the self-collection device, whatever it is that's being proposed, that's being brought to the FDA, is as good as collecting cells, equivalent to the standard, which right now is the LBP, to show that they are, basically equivalent, and we're going to do this in a doctor's office.

We just talked about, what do we get first, the self-collected samples, do we wait two weeks? Do we wait a day? That kind of comparison. And then once we show that the self-collected sample, it looks, to the cytopathologist, the cytotechnologist, as good as a good liquid based Pap, then we can take it out into the hinterlands.

But until that is done, I don't think we can move forward.

DR. CASTLE: Well, I -- my counter to that is, so we do a five year or a six-year trial -- it does take that long because the end points that you have to get, the number of people you have to enroll, the $20 million you have to spend on the trial to have the right end points, it's a six year trial.

Then at the end of the six years, you're then going to go show that these people will, or will not, which is another bunch of time. I mean --

DR. CUI: I actually agree, that's going to be a tough question to be answered. There are many, many --

DR. CASTLE: I'm again proposing that you combine -- because you know what population you have to reach, and so if you have something that doesn't work in that population, you're going to know very quickly. Right?

And the real fundamental public health metric should be diagnostic yield. Do the women use it, and does it provide disease, and you will know that very, very quickly, whether you get the 10 or 20 -- the prevalence of CIN-2, 3, in the population, in the United States, is around one percent. Probably higher in the special populations, probably about 1.5 percent, maybe 2 percent.

If you look at the breast and cervical cancer program, it's about two percent, so let's say that that's the -- closer to the truth.

So, if you do a thousand people, you should, if everybody participates, and you have good colposcopy, you should get 20 CIN-2, 3's. If you only get five, it's either because the method doesn't work very well, or they're not

participating, but you'll actually get to your answer quicker than a traditional clinical trial, and you'll have the right people participating.

So, I realize that I'm being highly provocative, but I have been doing this for a long time, I do this internationally a lot, and you actually have to think about different metrics for special populations, that are better metrics.

DR. CUI: Thank you so much.

So, let's move on to the next question. Maybe that's the second to the last question.

MR. KLEIN: I'm Phil Klein, GyneConcepts. As I mentioned earlier, I'm the inventor of a collection device. I would like to say that during our testing, field testing of our device, we almost followed an identical pattern that Dr. Conlen followed, unknowingly, the way we tested our device, and we found our results excellent.

We found that the individuals that we brought in, whether they were Asian, no matter what nationality or ethnicity, every single one of them had nothing but -- I shouldn't say 100 percent,

because we didn't get -- not all of them came, were willing to give us a post exam interview, but everyone that did were just thrilled by the ease and convenience, and how they liked the device.

As far as -- and this came up as I listened to you talk --

DR. CUI: Thank you --

MR. KLIEN: This is something we did, we actually had Pap smear testing done in our home, we got groups that came together, came into our home, our doctor came, very low key, but they came into the home -- we had several bathrooms, they all went into different directions, self-tested in a very non-threatening atmosphere, did their test, we got all the information, did all the post-op, and -- or post-testing interviews, and they left.

I think that is the way you go. You could go -- say, for example, say a Latino situation where there may be aliens that -- illegal aliens involved, what you do is you find somebody that's very responsible in that community, that they trust, you set up a mini-clinic in that home, and

do that -- have those people, like a Tupperware party, almost, have them come in to do the test.

DR. CUI: I think you will have an opportunity to speak during the public comment session.

MR. KLEIN: Okay.

DR. CUI: Let's move on -- if you allow, let's move on to the next question.

The next question is about unsat results. So, what to do with the unsat results. I think are we going -- are you going to expect an elevation of this unsat rate, if -- and then how to do with the unsat results.

DR. CASTLE: I would simplify Marina's diagram to normal and abnormal, and I would throw the unsats in the abnormal --

DR. CUI: Okay.

DR. CASTLE: -- (simultaneous speaking) that it's a high-risk population. You want it as simple -- simple, clear, and direct, is what my wife would say.

You know, you want to -- you want to keep the system simple, this is a high risk population; you

may never get another sample from them, so if you're going -- you know, colposcopy is a low risk intervention, so -- and you're not going to treat them unless you actually find CIN-2, 3, so given the complexity of saying, I'm sorry, you unsat, you know, trying to get them to sample again, or sample again in some time; no, I would err on the side of sensitivity, because of this -- their special needs -- they're higher risk.

DR. CUI: Okay. Thanks. Any other thoughts from the panel about unsat? Okay.

MR. KALAVAR: So this is Shyam Kalavar, FDA. So, I have a question following up to Dr. Castle's comment.

So, reporting cytology result as normal/abnormal, does it have any pathology practice implications?

For example, if you saw, in a self-collected specimen, high grade lesion, and simply reporting it as abnormal, do you see any problems with that? What would the follow up be --

DR. CONLEN: I'm not sure I understood what

you were asking, if --

MR. KALAVAR: I think it had to do with Dr. Marina's -- Kondratovich's -- one of the three options that she had that suggested reporting formats. Report all Bethesda categories, and then the second one was report it as normal --

DR. KONDRATOVICH: Abnormal and unsat and (simultaneous speaking) --

MR. KALAVAR: Yeah.

DR. KONDRATOVICH: -- abnormal.

DR. CASTLE: Well, so who are we reporting to? Can you clarify?

DR. KONDRATOVICH: To the patient --

DR. CASTLE: To the patient it's normal/abnormal. To the colposcopist, you absolutely want report out the --

DR. BOOTH: Give the Bethesda --

DR. CASTLE: Right.

DR. BOOTH: You have to give the Bethesda category to the colposcopist. Absolutely.

DR. CASTLE: Right.

DR. CONLEN: You have to be consistent --

DR. CASTLE: Particularly for HSIL, because they're going to want -- you know, if they don't see anything, they need to be more rigorous -- I mean, they have to dig --

MR. KALAVAR: Yeah. And what would the follow up be, and so --

DR. CASTLE: You have two reporting's. You have the simple, clear, direct message to the patient, normal/abnormal, and you throw the unsats into the abnormal for safety reason. You report to the clinicians the Bethesda System. I totally, 100 percent, agree.

DR. BOOTH: My concern is that -- so, for example, in the rare occasion that you're finding an invasive cancer in the patients, how do you follow that, if you're only reporting to the patient and you're just saying abnormal -- I guess, as a pathologist, and my care of the patient, I feel very uncomfortable with that.

Even though I don't want to tell the patient that they have invasive cancer, I guess, I feel like there needs to be --

DR. CASTLE: You could have a safety net.

DR. BOOTH: Yes.

DR. CASTLE: So, let's take -- let's play out her -- Christine's scenario. So let's say the lab gets the results, and they typically -- you know, they have normal/abnormal, and they could also have a flag in there where they say, I think I saw cancer, it goes to you, or you know, to the physician, and the physician then -- that's where the physician would have a direct intervention there, because that's -- you're now in an entirely different -- you need to get them into the cancer care system.

DR. BOOTH: Right. So my question is, who is ordering the test? I still -- we still don't know that.

DR. CONLEN: Well, we talked about this. We talked about the bottle, where you need to have physician over-sight. Before the test gets done, when the patient buys -- there must be a registration.

At that particular point, it then goes through

some of the -- then there's several different types of tele-medicine, or individual lab companies that have platforms that manage the test going to the laboratory and the result coming back, and that is called physician oversight, and you must have that.

You can't be telling a patient on Friday afternoon on a text that she has invasive cancer. All right? You could say, well, it's normal but we will contact you, and it is our obligation to follow up, make sure there is follow up care, and if it is normal to remind them what the criteria is to make them come back.

That's important, as well as education, when you have that moment.

So, no, I don't think the patient should be getting the report. You can tell them it's normal, that's fine, but there will be a follow up.

MR. KALAVAR: So if the result going out to the clinician as the actual Bethesda categories, then the study design would have to be

appropriately -- be appropriate, right --

DR. KONDRATOVICH: Yes, and -- like if I see, for physician it will important, like HSIL and Low-SIL, then everything should be evaluated. Yeah, this is very complicated study design.

DR. CUI: Yeah.

DR. CONLEN: You know, what you have to remember is (simultaneous speaking) --

DR. CUI: I just want to remind everyone, we only have three minutes left, so just to keep your comments or questions short.

DR. SCHIFFMAN: We published in JAMA that agreement on the Bethesda System among experts is marginal, you know, for some categories. So, I understand what your metric is even going to be, as what's acceptable between the self-sample, the Bethesda, and the reference Bethesda.

DR. KONDRATOVICH: Yes, exactly.

DR. CUI: Yes. Thank you.

DR. CONLEN: But we do deal with that every day in practice. Okay?

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. CONLEN: Well, that's a different story, but you know (simultaneous speaking) --

DR. KONDRATOVICH: (Simultaneous speaking) like how you can evaluate this, especially if you have only colposcopy results, like histology CIN-2, CIN-3's, and --

DR. CUI: How to correlate (simultaneous speaking) --

DR. KONDRATOVICH: Yes, and this is correlation, we know that it's very weak. Yeah, this is very different study design.

MR. QUICK: Mike Quick from Hologic, and one thing I was really pleased to hear Marina say was about least burdensome pathway forward. So that's really encouraging, as a manufacturer, to hear.

The one challenge that we haven't talked about, though, is -- which Dr. Staats talked about this morning, which was around the approval as a system.

And so, we've talked about collection devices, but yet they tie into various systems, and if we're talking about liquid based cytology, it's

either ThinPrep or Sure Path, and then there's combinations of whether it's prepared on which processor, first live preparation, and then how the slide is read, in terms of if it's imaged or manually read.

So, the complexity of these studies, while it's great to see a two by two chart up here that makes it look very simple, every new device that you're talking about from self-collection, also has to be validated with each processor, and each methodology of reading, which becomes very challenging, which I'd like to hear from the panel.

DR. CONLEN: Well, I mean, if you're obtaining cervical cells, and it's going into the liquid based vial, and it's being processed, it should be the same as if the clinician has been obtaining it.

Unless we're saying that it's not the same, and what I described earlier, I feel that it is the same.

So, although, I know what you mean by

validation; we want to make sure. There should not be that much difference, if we're -- unless, you know, there's some step in-between.

And, you know, there -- I don't think there needs to be a step in-between. I think the self-administered protocols can go into the liquid based, no matter what.

We talked about drinking it; childproof, you know, Tylenol. We have lots of toxins in our houses, so I don't see that that's an issue.

Then once it goes through the machine, we're going to get a result. It's going to aspirate cells. Hologic has a nice liquid based that eliminates a lot of the debris. It should be a nice clear picture.

DR. CUI: Okay.

DR. CONLEN: Unless there something that I'm missing.

DR. CUI: Yeah, I think our time is up. Just to take one more question from the audience.

DR. ANDREWS: Just to quickly address the concern about reporting abnormal results to women

themselves.

Again, I reference you to the example of mammography. The FDA approved self-referred mammography, whether it's self-referred or doctor referred, every radiologist has to give the patient a copy of their report, which includes whether it's normal or abnormal, and of course, there's options for referring patients who need referral.

So we have an example to look at.

DR. CUI: Thank you. Yes. Okay. So, I think, for that, we are going to conclude our panel discussion, and thank you very much for your helpful and considerable discussion. Thank you, audience, as well.

Now, we are going to move to public comments session, and I have a list of speakers who have registered to speak during this public comment session.

The (inaudible) already registered for this workshop. And I'm aware some of them -- some of you may not be here, so just have a look at the

list and then Shyam is going to announce the speaker, and then if your name is next just come up to the podium to get ready for your speak.

And I just want to remind you -- yes, if you can, line up by the side, that would be very helpful, so that we can have enough time for other speakers, as well.

So, I want to emphasize each speaker will have five minutes. Thank you.

So, we begin with the first speaker.

MR. KALAVAR: So we have Jeff Andrews from BD.

DR. ANDREWS: Yes, my name is Jeff Andrews, and briefly, I've been an OB/GYN for 30 years, and 20 of those years in academia. I'm also the former Chief Medical and Science Officer for the American Society for Colposcopy and Cervical Pathology, and I'm currently the Medial Director for Women's Health and Cancer for Diagnostic Systems at BD.

We heard 12,000 cases of invasive cervical cancer reported yearly. Fifty percent, or more, of cervical cancer in the U.S. occurring in women

who are under screened or unscreened, and these 8 million women who are less likely to undergo cervical cancer screening be sub-grouped.

Roughly one-forth of the women without health insurance, or without a regular healthcare provider went unscreened, and other associated risk factors in the U.S. that we've heard about are living in the southern states, Native American, Native Alaskan, Asia Pacific Islander, living in rural areas, culturally and linguistically diverse women, survivors of sexual abuse, women with disabilities, women who have experienced female genital cutting, and LGBTI women.

Other factors include inter-personal barriers, embarrassment, anxiety about the procedure, fear of the results, mistrust of the healthcare system, too busy, lack of transportation, and lack of knowledge.

These women who are not screened as often as recommended are likely to benefit from a self-collection option.

Data from randomized trials have demonstrated that testing for HPV is amore appropriate and effective method of screening for cervical cancer than cytologic screening. The cervix is not the best target, and cytology is not the best self-sample test.

Self-sampling for HPV is a convenient and cost-effective method to increase screening population among hard to reach women.

What will the benefit be? For every one round of HPV screening using a self-collected sample, it would reduce cervical cancer risk by 41 percent over a woman's lifetime, when tested once between the age of 30 and 40, compared to the risk if she remained unscreened.

Will cell sampling work? There's at least ten years of cumulative evidence that HPV testing on self-samples is an effective alternative to protect non-responders in cervical cancer screening programs.

Will women accepted self-sampling? There's a high acceptance of, and positive attitudes

towards, self-sampling among hard to reach women. Providing HPV self-sampling kits to never screened and under screened women has been shown to improve screening participation in more than 36 international studies.

Will the test results be safe and effective? A recent systematic review, and two other independent meta analysis, indicated that testing for high risk HPV on self-collected vaginal samples has equivalent sensitivity, and similar or lower specificity, as cytologic examination of clinician collected cervical samples.

How will women get the results and understand the results; what will be the system or program? How will women access clinical professional advice and care, and how will that provide or acquire the self-sample test result?

The FDA may require that there be a documented method for ordering tests, reporting results, tracking and monitoring rates of detection, not detected, and unsatisfactory samples.

The FDA may require the testing be performed

at an accredited lab. The lab order could be generated by the women's clinician or by a program; that program could be national, state, or regional, or she could be self-referred.

Example of regulatory rules, programs, and guidelines exist now in Finland, Denmark, Australia, and the Netherlands, and by the way, all of these countries address the concern of switching. A uniquely American system and program will need to be developed for the U.S.

And, lastly, how to triage the results. A conventional method is to send the positive HPV sample result to an appointment with a clinician for an LBC clinician collected sample. However, there's a concern that non-attenders will not follow up, and additional testing would impact cost effectiveness.

By 2020 we'll have additional information available to triage the result, to determine whether the woman should have more aggressive reminders to follow up with a clinician.

Diagnostic triage tests available in the near

future include extended genotyping and E6, E7 oncoproteins. Diagnostic triage tests that may be available within the next few years include automated severity score of cervical cells, KI-68 P-16 immuno staining of cervical cells with automated qualitative result, and DNA methylation.

In summary, I encourage the FDA to provide a pathway to providing under screened women the option of self-sampling for cervical cancer screening. Thank you.

MR. KALAVAR: So the next speaker we have is Charles Lucher from GyneConcepts, but I guess Ms. Klein is going to take his place?

MS. KLEIN: Right.

MR. KALAVAR: Okay. Betty Klein.

MS. KLEIN: I'm Elizabeth Klein. Mr. Lucher and Mr. Skibell, both this morning had 102 temps, they both were diagnosed with the flu, so they weren't allowed on the airline, which we loved. So, we are here to speak, basically, as to what they were going to say.

It's very hard to add anything to what I've

already heard. (Inaudible) everything that has been said.

We come from the private sector. I do want you to know that we are currently in the FDA, embarking on another clinical trial. We have been able to have a good relationship, and we have been very fortunate with our reviewer, that he has been helpful in giving us direct information, and telling us when we weren't on target.

So, there's not a lot to add. We know that there is a tremendous need for us to find a way to screen the underserved, and even those women that are -- you know, they're bright, they're intelligent, they work a lot, they don't want to come in. There are a lot of reasons; you've heard all those reasons.

But I think it's incumbent upon us, in the private sector, to be a partner with the FDA, and to do our part to share and help you get us through this process, tell us what you see, what you don't see.

We've all heard from the panel; these are the

experts, these are the people that know what needs to be done, so that we're all safe and secure. This is their job and we don't want any less than that for our people or for our company.

So, no further comments from us, other than thank you for the opportunity to be here, and thank you for your conference. You did a great job. Thank you.

MR. KALAVAR: So, speaker number four, Sean Boyle from Roche has yielded his time, we'll move on to speaker number five, Barbara Crothers from ASE.

DR. CROTHERS: Yes, my name is Barbara Crothers, I'm a practicing cytopathologist, and I have over 30 years of experience in women's health and GYN oncology, as a diagnostician, as well as general pathology.

I'm also the current President of the American Society of Cytopathology, and I'm here to represent the interest of our cytopathology community and our patients.

We're the largest organization of

cytopathologists and cytotechnologists dedicated to the cytologic method of diagnostic pathology in the service of patient health and well-being.

The Pap test has been the most successful cancer screening and prevention test in history, and this sets a very high bar for alternative methodologies.

In the United States over the last 70 years we've constructed a very robust regulatory and quality framework that further ensures the high value of that test, despite its low cost. The test relies on proper collection, and processing of cells from the target site, the cervix.

Any self-collection device that requires a cytologic examination of collected cells as an interpretive test, must ensure equal or superior specimen collection to the current healthcare provider collection standard.

But as a community, I want to say that we really applaud the efforts to capture under screened and unscreened women by providing cervical cancer self-collection methods, and we

recognize that these devices may overcome the innate cultural and economic barriers to screening.

Tests using self-screening devices maybe better than no test at all, but they're not the same as an office visit with the physician, with specimen collection by the physician, examination and clinical information surrounding the patient's health. These are components that are necessary for the interpretation of any laboratory test.

And I know a lot of people like to think of it as a black box, and you put it in a machine, it comes out an answer, molecular test or not, that is not what a laboratory test is, and the best patient care requires more than that.

So, what's still unclear to me is how, if we do introduce self-collection devices on the market, how we do confine them to a special population. I mean, this is a separate standard of medicine, essentially.

You're saying that this population, because they're underserved and under screened, deserve a

lesser strength test. So I think the standard of the regular test that we're using now, is the proper standard that should be overcome.

So, our concerns are that women may opt of clinical visits, and opt into self-collection for reasons of cost and efficiency, with the potential outcome of increased cervical cancer rates, because they may just decide that once is enough, and I'm negative, and that's good.

Good specimen collection is a critical component for accurate test results, regardless of the test.

And HPV tests are also not fail proof; up to 25 percent of cervical cancer have been reported as HPV negative. And women that have already lost that clear message of an annual Pap test to prevent cervical cancer, along with the screening extension of intervals that have been promulgated by professional organizations, just may not get or take another chance.

The United States also lacks an organized screening cancer program that requires

registration, and that ensure regular screening and follow up. We are, essentially, an opportunistic system.

And, finally, without the companion of cytologic examination of cells, colposcopists bear the burden of the pre-cancer diagnosis, and colposcopy with biopsies, the so-called gold standards in detecting pre-cervical lesions, is itself fraught with its own interpretive problems, and lacks an organized quality assurance system or oversight.

So, we have concerns that a combination of these factors will increase incidence of cervical cancer, and that we will learn the hard-earned successes that we've achieved over the last seven decades with the Pap test.

But I thank you very much for your time, and the opportunity to speak here. It's been a wonderful session. Thank you.

MR. KALAVAR: So our next public speaker is Kainat Ishteyaque, and -- from NHSRC -- is the speaker here today? No, it doesn't look like it.

Okay.

So, we'll move on to Alex Rudolph from Personal Health Management LLC.

MR. RUDOLPH: Thank you for the opportunity. Perfect, I won't need it all -- most of what I have to say has already been said. So, I'll just kind of go over a little overview of what -- the topic I came to speak about is the feasibility and benefits of self-collection for Pap tests.

I think it's been stated that some of the obstacles that we have to overcome involve after the fact, after the collection; disseminating the results, the logistics, that sort of thing, and I believe those are obstacles that we could easily overcome with, you know, end to end oversight, as Dr. Conlen was mentioning.

Home diagnostic and monitoring of various disease states has become more prevalent in recent years, as we all know, anywhere from pregnancy to HIV, to rectal, to urinalysis, and this can all be attributed to patients more conscientious -- their more conscious role in their own health

management. Their busier lifestyles, concerns for privacy, etcetera.

So, we all kind of agree that the future of healthcare is somewhat based in these home diagnostic solutions.

It also, obviously, what Mrs. Felder said, it eliminates the usual proding [sic], prodding, that is associated with a doctor examination, minimizing the anxiety associated with the testing process.

And most importantly, and I keep going back to this, it's tests like these that will really empower women who are not under the care of a physician by providing access to these important health screenings.

As far as physicians, clinics, and MSO's go, we believe they could utilize this as a patient requisition tool, a patient retention tool, and most importantly, a patient re-engagement tool for those who are sitting on the sidelines, and you know, that's a lot of the 4,000 that we've talked about, that's been mentioned a lot. Those are the

people we're trying to get off the bench, and back into the game.

As a member of a medical diagnostic device company, we have access to a lot of surveys. I know Dr. Conlen brought up thousands of women, and the one thing that's pretty consistent, is the genuine excite me see from women when discussing the possibility of self-screening for Pap and HPV.

It's palpable, it creates a very visceral reaction because, obviously, the convenience, the no appointment, not taking off for work, the privacy and discreetness. Women can utilize this test when and where they choose to, at their own choosing.

It appeals to -- across the board, and a range of social and economic groups, and most importantly, given them an opportunity to get screened when they normally wouldn't.

Because of the self-collection and privacy, that crosses the social, economic, cultural, and religious barriers, and empowers women to take control of this crucial aspect of women's health.

It opens doors and sparks -- it speaks volumes, excuse me, to being able to -- to be able to screen women in urban, suburban, rural areas, and create further outreach programs.

Thank you very much.

MR. KALAVAR: Okay. Our next speaker is Arthur Fournier from University of Miami, Miller School of Medicine.

DR. FOURNIER: As you can see, I'm an older physician, when poor handwriting was a badge of honor. So when they were taking my name off, they spelled it wrong, because I probably scribbled it, it's F-O-U-R-N-I-E-R.

I have had a career at Miami and in Haiti dedicated to teaching and developing better systems of care for poor patients. I grew up poor. My father died at age 40, and left my mother a widow with six children.

In Miami, and underserved communities, and in Haiti, the problems of cervical cancer and sexually transmitted infection preferentially afflict the poor.

And in Haiti, I've come to work with, very closely, Dr. Paul Farmer, who makes the case that we need a preferential option for the poor, and I think cervical self-sampling -- excuse me -- self-sampling is, not only a preferential option for the poor, but actually, a preferential option for all women.

Because, let's face it, as Dr. Castle said, who wants to get up in stirrups, and let me tell you, I taught medical student for generations how to take Pap smears; there's a lot of operate variability in how take the Pap smears.

Now, as an aside, with regard to research design, a huge issue is operate variability, and it think building in controls to see that the procedure is standardized is going to be a key thing.

On the narrow question of research, I agree complete with Dr. Castle, also. Yes, you have to demonstrate safety and efficacy, but perhaps there are different ways, population based ways, of demonstrating safety and efficacy.

And efficacy has to factor in other things that are narrowly discovered by clinical trials. First of all, how they lower the burden of other diseases.

The number one thing I want to talk about right now is the need for multi-testing. Clinicians need -- the role of self-sampling ought to be to provide clinicians with the maximum amount of information they need to take care of their patients.

To do that, I think we need to have a team approach. A critical part of that team, and we've learned this in Haiti, we've demonstrated it Haiti, and I've taken it back to Miami, is to integrate community health workers for -- as peer educators and peer facilitators of the care.

It makes no sense to screen for cervical cancer, either with conventional exams, or self-sampling, unless you also screen for sexually transmitted infections. They run in the same pack.

So, I thank the FDA for putting this together.

I see a role for cytology. I think we need to do more research. I really am impressed to meet Dr. Conlen and hear the progress he's making. I think this is the way to go.

We absolutely have to multi-test and co-test, and it can be done with variations on the tips, and the collection methods, and auto analysis, so if you get a larger number of cells, I think we can find a role for self-sampling with -- for cytology, in addition to molecular testing.

The safety and efficacy of molecular testing has already been proven, so I think that part of the discussion is over. It's just a question of how cytology fits in, and whether cytology can also be included in a self-sampling package.

Thank you.

MR. KALAVAR: Our next speaker is Jennifer Smith from the University of North Carolina at Chapel Hill.

MS. SMITH: Okay. I want to just thank the panel for this session today, and all of the lively discussion that we've had, and a couple of

the slides -- I think Mark started his talk saying some of these concepts have been repeated, and so I'm going to probably quickly move through the slides as quickly as I can, without trying to repeat others who have made very good points.

When I first started working on self-sampling -- I've been working on self-sampling in the U.S. and internationally for many, many years, and we started working North Carolina, Phil Castle said, well, why don't you go and interview women who haven't been screened and find out why they haven't been screened.

So, that's what we did; we interviewed women who hadn't been screened in North Carolina, and most of them, are uninsured and Medicaid patients, who basically said, I have no insurance and, therefore, screening is not for me.

So, we went on the next -- so I think the imperative question is, if we have these under screened women, and mortality is occurring upon them, how can we optimize approaches to increasing screening rates among these under screened that we

discussed?

So, our series of My Body, My Test studies conducted in North Carolina to assess the feasibility and acceptability of home based self-collection among these low-income under screened women, high risk for cervical cancer.

I'll note it's striking to me how few studies have been done in the U.S. among the under screened, whereas our guidelines and recommendations are largely based on insured populations.

So, I think this is actually novel when you think about the population that we've been able to recruit.

We had them self-collect cervical vaginal cells that -- at home with the Viba-Brush from Rovers that was collected and placed in APTIMA media, which is safe for mail provision. The women returned the samples by mail for HPV testing with APTIMA, and then they received their self-test results by telephone.

At no point did we send results by mail,

unless we were unable to reach the woman by telephone, but we were successful in our most recent study, in getting the results out to 95 percent of the women in our study, which I think is pretty phenomenal.

And then, in terms of referring women to clinic (inaudible) screening, that's the next step, of course, and we had to, in our phases of our study, have clinical partners who were working with us.

It was really important for us, as we launched in a county, to find a clinical partner, who would be able to work to receive these patients.

So, our population was those unscreened, like I mentioned, 30 to 64 years of age, they were relatively poor, uninsured, under insured, or on Medicaid, no history of co-testing.

When we first started the studies, co-testing was actually not available, and they had to have intact cervix, and not be pregnant. The median time since last Pap was seven years.

So, we had these flyers that we distributed

throughout community partners, and I think one thing that -- when you think about a mailed intervention -- I think this is a really mixed community based outreach, and then mailing, because, as we've discussed in this session, we don't have a screening registry, in order to identify women who haven't been screened, according to schedule. So, we were working with our partners in the state.

We also have had very good success with Craigslist. We post in the job section of Craigslist.

I know that Dr. Castle mentioned Facebook, email; we have not had success with Facebook. We tried very hard. We're finding that this population is probably not -- not the best recruitment strategy for this really under served and under screened population.

We have had some success with 211, when people call for rental assistance, with United Way, and then we had a lot of success with, also, word of mouth recruitment. Women in the study referring

others into the study, as well as recruitment within our clinical partners.

I would also say that we spent a lot of time trying to develop our materials with Dr. Noelle Burel (ph) on health behavior to really have very simplified messages, and I'm happy to send people kits, or share our information to anyone who's interested.

So, this is a very small study, and I appreciate Dr. Schiffman's comment about larger studies, a need for larger studies, in the U.S. I think, though, there's been very large studies in Asia, as well as Europe, that show very good results of increasing screening, particularly in Europe, among the under screened, with the self-collection kit opportunity.

I know that in the Netherlands and Denmark, they're also moving forward in their national programs with an image of self-collection being right, front, and center.

So, just to think about our results, though, you know, in the small sample size, and this is

phase two, My Body, My Test 2, 284 women received their self kit, they returned it, 80 percent return their self kit.

Again, these are women who expressed interest in receiving a self kit. It's not the same as just sending a self kit out, and so that is explaining some of the higher percentages that you're seeing here, that may not map onto the results that you might expect, if you just mailed everyone out a self kit.

So, and then we, of course, had our clinical appointment being an important indicator.

I will say that in this study, I was interested in comparing clinic attendance among self-test negative and self-positive, so we referred both groups into the clinic.

We had stronger messages for the negatives than the positives, but that's now how you would actually roll this out in a real practice, in our current My Body, My Test 3 phrase of the research. We actually have just the positives being referred into the clinic.

But I will say, there's been a lot of questions about whether it's feasible to identify under screened women. Is it feasible to send them the kits; do they send them back?

Is it feasible to actually have these women who are outside of screening intervals; in our case it's been seven years, come back to the clinic?

And are results 86 percent, clinic follow up rates, among under screened women, who are self-test positive, I think answers that question.

So, we have had rates of CIN-2 in our studies, on the average of two to three percent, and this is in phase two, we have a three percent CIN-2 rate. This is an extraordinary high CIN-2 rate. I actually had them double check it a couple times to make sure that this is truly, indeed, the rate.

Again, these are under screened women, these are rates of CIN-2 that are comparable to those that you see in global setting.

And I call this global health intervention research. It really is. Our sisters and our

friends, right down the street in North Carolina, and in many states, in every state that we live in, there's a geographical area that has this high incidence pockets, and this is the group that we have to focus on.

So, if you look at the self-test positivity, again using the APTIMA test, we found that all of the high-grade lesions, and that also among all the CIN-2 histologic confirmed cases, were all self-test positive with the home sample. So we missed no CIN-2 cases.

So, I think we have a prerogative to really think about this data, as it relates to the interventions that we want to think about among the under screened, as has been discussed in the previous discussions.

Women found it to be very convenient, easy to use, private, and that was very high acceptability about receiving the kits in the mail, returning them. These are all data that are published now in STI's and STD's.

So, I just wanted to say that we really think

that the self-sampling screening for HPV may allow programs with restrained funding to increase their screening coverage, while maintaining nearly equivalent sensitivity for high grade detection, as compared to co-testing, and programs like the National Breast and Cervical Cancer Early Detection Problem -- program have funding restrictions, and in some states the program runs out of funding in the year, and women are turned away from services, as they are in North Carolina.

These limited budgets are difficult programmatic decision to be made between cost of screening per patient and the number of women screened, and we think that in the United States that self-collection certainly has a role, and particularly in global settings.

Thank you.

MR. KALAVAR: Okay. So our last speaker is Edward Evantash from Hologic.

DR. EVANTASH: Great. Thank you to the FDA, and to the esteemed panel, and to the audience. This has been a wonderful session today, and I'm

happy to be the final speaker.

My name is Dr. Edward Evantash. I am the Medical Director at Hologic, Vice-President of Medical Affairs. I've been an OB/GYN for over 20 years, and many of you know Hologic has been the industry leader in cervical cancer screening, since the introduction of ThinPrep liquid based cytology in 1996.

What we've seen in the last 20 years has been an evolution in screening techniques that have further contributed to, arguably, the greatest success story in cancer screening.

Cervical cancer, previously the number one cause of cancer death among women in the United States is still associated with just over 4,000 deaths per year, but has been reduced to the 21st most common cause of cancer in women.

The current guidelines for cervical cancer screening provide the greatest detection of, and reassurance against developing disease.

In women 30 to 65 years of age, co-testing with Pap and HPV is the preferred method of

screening, and is associated with the lowest cumulative probability of CIN free and cancer.

We understand that, regrettably, a sizable number of women in the United States are not screened, or unable to be screened within the recommended time intervals, and that this contributes to the inability to eradicate this disease.

What remains unclear is the impact of Pap self-collection on the overall incidence and mortality of cervical cancer, and that is with the reduced sensitivity and specificity of self-collection of Pap provide greater benefit.

With the introduction of HPV vaccines, and advanced HPV technologies, we will continue to see positive impacts on the incidence and morality of cervical cancer in the United States, and what remains elusive is reaching those populations of women unable to obtain protection against HPV, and get regular screening against the disease, and perhaps self-collection of Pap will allow us to address this subset of women at risk. But at what

cost?

Women current screened in the gynecologist's office may choose self-collection over clinician testing to avoid the discomfort of the GYN exam.

What impact will this have on the general population of women in the United States who do receive regular care, and currently are seeing the lowest rates of cervical cancer?

The consequences of introducing a home test can, perhaps, be best understood in the context of HIV testing and genetic testing, but recognizing that women see preventive healthcare as a corolate to their Pap tests, means that changing the method of collection may have implications on health of women beyond just cervical cancer screening.

We need to be sure that the goal we seek to achieve with self-collection is extending the reach of cervical cancer screening to the unscreened and the under screened population of women, while not compromising patient health by moving the screened population off the GYN exam

table, which may reduce the frequency of other important diagnostic tests, or result in reduction in sensitivity and specificity for cervical cancer screening.

To be clear, we at Hologic are committed to contributing to seeing the end of this preventable disease. Reaching the unscreened and the under screened population at risk for cervical cancer is perhaps one step closer to achieving that goal.

But we believe that a cautious approach, backed by the appropriate clinical studies will be critical to assure that we never compromise the health of women, and we don't substitute what works with something that doesn't.

Thank you.

DR. CUI: I want to thank everyone who contributed to the public comment session. Thank you so much for your comments.

And with that, I'm going to introduce Reena Philip for the closing remarks.

DR. PHILIP: Thank you, Cheng.

I'm sure you'll agree with me that we had a

very productive workshop on self-collection devices for Pap testing. I will go over some of the main points we heard in the morning and afternoon sessions.

So, in the morning we heard 85 percent of women have access to cervical cancer screening, and 15 percent still do not get screened. There are 12,000 new cases of cervical cancer annually, and 4,000 deaths.

And the risk factors for cancer are 50 percent do not get screened for various reasons, such as lack of health information, coverage, no access to clinics, some religious reasons, cultural reasons, etcetera, and the rest is a combination of false negative cytology test results, loss to follow up, medical mismanagement, and difficult to detect by cytology, including sensitivity issues.

So, will a self-collection improve cervical cancer screening? And there are no adequate data currently available in the U.S. Most literature is about self-collection, is for HPV testing.

So, existing practice is trying to gauge

poor sensitivity for cytology, some were better for HPV compared to provider collection.

The main concerns that we heard today; will the interaction of the self-collection device harm more women than it will help? Women that normally get screened may choose a self-collection device path for testing, could be an issue if the device does not perform to the level of current standard of care.

And we also heard about specimen adequacy. Study shows that the lack of endocervical component in provided collected specimens does not affect result, but how will we know that the transformation zone was sampled with the self-collection device, should be -- is there a need for look into the endocervical cells [sic].

Should the system be evaluated as a whole, in reference to how the FDA approved systems have been evaluated to date?

We also heard about issues about testing and result reporting in the case of self-collection devices. How will it be labeled? How the patient

ID will be done, HIPAA issues. Where will the patient send specimens and who will get the results? We also heard some of the DTC issues, direct to consumer issues. Who is responsible for interpretation and reporting to patients, and some of the legal issues.

And there were some safety concerns that -- brought up, including the methanol and ethanol based preservatives. You know, kids drinking the media.

No concerns were indicated with inserting the device in the vagina.

So, in conclusion, we also heard that a large-scale study will be needed to assess the safety and effectiveness of the device.

We heard access and reimbursement are the two main issues.

In the afternoon there were talk about the clinical study design consideration. The intended use population should match the U.S. population, and the choice of gold standard for clinical study colposcopy or cytology, and with the majority

(inaudible).

So, during the panel discussion some of the questions that Cheng raised to the panel; first one was about the non-responders' question. Should they be included in the performance studies, and we heard women that are non-responders, non-participants, should be included in studies. It's likely that they'll have higher incidence of disease.

We heard reimbursement issues. What to do with the abnormal Pap results for the women without coverage access?

We heard about concerns having drop outs, if they must go to the clinic for collection of cervical samples for comparison in the study, and there was some argument on focus should be on demonstrating that the device works, rather than focusing on including non-participants first.

Then the two collection devices and the study (inaudible) what would be the minimum maximum acceptable timing intervals between the two collections, self-collection versus the

professional collection, and I think we heard two weeks may be okay.

And the there were question about the gold standard and colposcopy versus cytology, and colposcopy followed by biopsy may be preferable, that’s what we heard.

And we also heard about issues about how to report studies; normal versus abnormal, or should be reported Bethesda criteria.

A question that came up in both panels were who order the test? Who receives the test? And how the test results should be reported; should they be reported to the physician or to the patient.

So, anyway, at the end we all agree that there is a need to serve the underserved population, the under screened and unscreened women, and to study the design need to be well thought out, that eventually leads to a marketing device that is safe and effective.

The study design should support the intended population of the devices.

We heard lots of good feedback at this workshop, which we will try to incorporate when we work on the study designs with the sponsors, and so that we can get a self-collection device for the Pap testing into market.

Thanks to all of you for attending this workshop. Special thanks to the presenters and panelists for a very productive discussion, and all the good points you brought up, and a very, very special thanks to my FDA colleagues Shyam and Cheng, and Eunice, and also the others who helped, Francisca, Jacob, Debu, and Mario, who helped to make this workshop really successful.

Thank you all, and have a safe trip back.

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I, Natalia Thomas, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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