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https://reachmd.com/programs/cme/panel-discussion-impact-extended-hpv-genotype-testing-current-cervical-cancer-algorithms/8111/

Released: 05/31/2016
Valid until: 12/31/2017
Time needed to complete: 30 minutes

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Panel Discussion: Impact of Extended HPV Genotype Testing on Current Cervical Cancer Algorithms

Narrator:

Welcome to CME on ReachMD. This segment, **Panel Discussion: Impact of Extended HPV Genotype Testing on Current Cervical Cancer Algorithms**, is sponsored by Omnia Education and supported by an educational grant from BD Life Sciences. Your experts joining us today are Dr. Warner Huh, the Margaret Cameron Spain Endowed Chair in Obstetrics and Gynecology, Professor/Division Director of Obstetrics and Gynecology at the University of Alabama at Birmingham, in Birmingham, Alabama, and Dr. Thomas Wright, Professor Emeritus of Pathology and Cell Biology at the New York Presbyterian Hospital at the Columbia University Medical Center.

Dr. Wright:

While specific clinical situations exist in which co-testing of HPV primary screening for cervical cancer might be preferred, data continues to accrue that infection with high-risk genotypes other than 16 and 18 increase the risk of developing CIN 3 and invasive cervical cancer. Other data, evaluating women with ASCUS provides support for extended genotype identification beyond HPV 16, 18, and 45. This is to be used as a means to improve disease management. Join us today as we discuss the potential of extended HPV genotype testing in high-risk HPV screening for cervical cancer, and the impact that this may have on the current cervical cancer algorithms.

Joining us today via Skype is Dr. Warner Huh. Warner, thank you for joining me today. I think this is going to be a great discussion.

Dr. Huh:

Tom, it's great to be here with you today. Let's go ahead and start the discussion. So, Tom, as you know, over the last 5 years there has been a general acceptance among clinicians in the United States that cervical cancer screening, for most women, needs to incorporate HPV testing, either as co-testing or what we call primary HPV screening testing by itself. Are there specific clinical scenarios in which you believe either co-testing or primary HPV screening would be preferred?

Dr. Wright:

That's interesting, Warner. I think the first point, which is really important to make, is that both co-testing and HPV primary screening are safe for women. As you know, and I'm sure our audience knows, there are different intervals for primary HPV screening and for co-testing. With co-testing, the interval recently was expanded out to 5 years. So, for women 30 years and over in the United States, they can be co-tested with both HPV and cervical cytology at a 5-year interval. For women who want to have HPV primary screening, that's got a slightly different indication. That is for women 25 years and older, so it starts 5 years younger than co-testing, and the interval is

only 3 years. Both are safe and effective. So, when you say, is there a certain clinical situation where I would prefer primary over co-testing, the one which comes to mind immediately is in the women 25 to 29. There, co-testing is currently not indicated by any of the professional societies, whereas HPV primary screening is. And I certainly believe, because of the very high prevalence of disease in women 25 to 29, that it would be quite useful to incorporate HPV testing. So I would recommend HPV primary screening in this group.

The other area where, when I'm comparing co-testing versus HPV primary, is that when you take interval out of that discussion and you say, at a given screen, which is going to be more sensitive, it is going to be co-testing, because you've got 2 tests. So, if a woman walks through the door, you have no idea of what her screening history is, she's 35 or 40, she may not have had a Pap in the last 10 years; in that situation I would prefer to co-test because I get a little additional sensitivity by incorporating the cytology with the HPV. Other than that, though, I think both are well-accepted, safe, and effective.

Dr. Huh:

So, when you look at, in addition to type 16, now there are different assays that allow us to identify women infected with HPV 18 or 18 and 45 together. Is there a specific rationale for identifying these genotypes the same as for HPV 16 and what is that impact of including 45 together with HPV type 18?

Dr. Wright:

It's clear that HPV 16 is a different bug than the other high-risk HPV genotypes. HPV 16 is associated with the majority of cancers. HPV 16 develops lesions quicker than do the other HPV genotypes; the lesions tend to be bigger and they occur in younger women. So, I think everybody recognizes that we have to have HPV 16. Once you go beyond HPV 16, you start looking at the rationale for any additional genotype; 18 you can make a very good rationale for including that, because it's the second-most common HPV genotype in women with cancer, it's quite commonly found in women with adenocarcinomas, and we know adenocarcinomas are particularly hard to identify using cytology. So, I can make a good rationale for including 18 based on its association with adenocarcinoma.

HPV 45, when we look at the large series of invasive cervical cancers, we find HPV 45 is not nearly as important as HPV 16 and 18. Moreover, when we look at CIN 3 lesions we rarely find HPV 45 in CIN 3. There are other genotypes which are more commonly found in CIN 3 lesions than HPV 45. So it's hard to make an argument that we want to include HPV 45 in our list of high-risk genotypes. The reason it has been included is that some assays find it very difficult to separate 18 from 45. So they can't identify 18 without cross-reacting with HPV 45 and that's why some assays pool 18 and 45 together. What's a negative impact of including HPV 45? Well, it's like any screening situation. You want maximum sensitivity while maintaining maximum specificity. And this actually gets hard to do with cervical cancer screening. So, when we include HPV 45, what we actually do is send a small percentage of additional patients on to colposcopy who are at relatively low risk for having either CIN 3 or invasive cervical cancer. And I, personally, think it would be preferable not to include 45.

Dr. Huh:

That's interesting.

Dr. Wright:

Dr. Huh, the IARC, which is the research cancer arm of the World Health Organization, recognizes today 13 high-risk HPV genotypes as potentially causing cancer in humans. There have been a number of international case control studies that have studied the risk of invasive cervical cancer associated with each of these different high-risk genotypes. Can you discuss the risks associated with non 16/18 genotypes?

Dr. Huh:

Yes, that's a great question, Tom, and as you mentioned earlier, we already know that type 16 and type 18 are associated with a pretty considerable and clinically significant risk of developing invasive cervical cancer in a woman's lifetime, particularly those women that

have a persistent infection, not just that one isolated infection that goes away after 6 or 12 months, but women who have been infected for 12, 18, 24-plus months. The interest now is what about these other types and when we look at data that is from the United States, we lump all of these other high-risk types out of 16 and 18 separately and what we do know is that risk is lower. So, one of the problems associated with these case control studies is that what we know is that, for instance, type 16 is the most prevalent type, so it's really common, we've got great data on it. So once we get past these more common types, we just simply have less data to indicate what those risks are, but I think what we're learning now is that there are other types that are outside of 16 and 18 that are potentially associated with a higher risk of developing pre-invasive disease of the cervix and cervical cancer. I think the key thing is that what we recognize is that when you stratify it by genotype, we can actually now start really looking at risks that are at an individual **woman's** level in terms of whether or not they need to be followed over time, or they need immediate colposcopy, or even more so they need immediate treatment. So, it's no longer an issue of whether or not we look at just the entire panel of women who have a high-risk HPV type. What we now want to know is the specific genotypes, because we've really amassed some considerable data, both in the United States and in Europe, that allows us to look at specific genotypes, maybe different combinations of genotypes, to figure out whether or not an individual woman needs immediate colposcopy or maybe even immediate treatment, or whether or not that woman can be followed over time. And it's pretty powerful information. So, the hard thing is to get that information to clinicians and make it practical and clinically useful, but I think, Tom, you and I both probably agree, it's more than just probably about 16 and 18. What we know is that various experts in the world have published data that looks at other types and combinations thereof that might allow us to stratify this risk for women in terms of what happens next after they get their test results.

Dr. Wright:

Dr. Huh, this concept that we want more than just 16 and 18, or 16, 18, and 45. Recently the New Mexico Path HPV Registry evaluated the risk of high-grade cervical disease associated with different high-risks HPV genotypes. How do their results compare with the international case control studies of invasive cervical cancer that you just discussed?

Dr. Huh:

So, that's a great question because it's a follow-up to my earlier answer to your last question, Dr. Wright, and what we learn is, from the New Mexico registry is, again, maybe 16 is not just the only type that we're interested in and their data indicates that perhaps types 31 and 33 as well as type 16 may be equally important in terms of this discussion, in terms of risk. In terms of risk of whether or not that woman needs immediate colposcopy, or if they're negative for those types they can be followed over time. And I think that's really the big take-away message from the New Mexico registry is that, I think we cannot restrict our knowledge just to 16 and 18 and say that these are the only 2 types that we're going to look at. I think that we need to start looking at these other types and as I am sure we will discuss over the course of this is that, I think the combinations are actually probably equally important as well.

Dr. Wright:

The concept that we need to go beyond 16 and 18 really needs to be supported by pretty solid data, Dr. Huh. What type of data are we going to have to get to be able to expand our horizons?

Dr. Huh:

Dr. Wright, that's actually a great question because that actually goes to what I was about to ask you. And what I wanted to as you is that, prospective follow-up studies have shown that both in the United States and Scandinavia that different HPV genotypes are associated with different risks of developing CIN 3, pre-cancer of the cervix, and invasive cervical cancer. Can you describe how these follow-up studies and their key findings for us, and can you also tell us how might these findings change the way we ultimately use genotyping for cervical cancer screening?

Dr. Wright:

Absolutely, Warner. The question, as you phrased it, actually though has a basic problem that we have to address first and that is, are we looking at CIN 3 development or are we looking at invasive cervical cancer development? As you know, but many of our readers

may not understand, there actually is a fair difference in the genotype distribution between CIN 3 and invasive cervical cancer. HPV 18 is a great example of this. When I look at CIN 3 lesions, HPV 18 is not one of the most common types and yet it is the second most common type in invasive cervical cancer. Our problem is, is that even though we would like to use the development of invasive cervical cancer, we really can't because there are just not enough cases of cervical cancer to allow us to do a good study. So, we're stuck with using CIN 3 as a surrogate for invasive cervical cancer. The prospective studies which have looked at the development of CIN 3 lesions have been all over the world. One of the better ones was one that was done by the National Cancer Institute in Portland, Oregon. They took women who were enrolled in Kaiser Portland, and they followed them up to 15 years. What they found is what you would expect. HPV 16 is, by far, the most common type associated with the development of CIN 3 and cervical cancer, but they had too few cervical cancers to really pull that out specifically. So, we're talking about CIN 3. The second most common type associated with the development of CIN 3 was HPV 18 in their study. But after 15 years of follow-up they also found that HPV 31 was associated with quite a few cases of CIN 3. Other high-risk HPV genotypes had a very low association with subsequent development of CIN 3 lesions. So that's the NCI's U.S. study.

In Europe, a similar study was done in Denmark. They took slightly younger women and they followed them up for up to 12 years. What they found is, again, the most common HPV type associated with the development of CIN 3 is HPV 16 and, in fact, 12 years after entry into the study about 25% of women who had HPV 16 at entry were diagnosed with either CIN 3 or invasive cervical cancer. Slightly underneath the risk of HPV 16 was HPV 18 which was grouped together with HPV 31 and 33. Other high-risk types had very low risks in the Danish study. So, what this is telling us, I think, is that clearly we have to identify women with HPV 16; because of cancer we want to identify women with HPV 18, but when we talk to what you were talking about earlier, identifying risk groups, HPV 31 and 33 both look like they're quite important.

Dr. Huh:

So, and along those lines, I guess the question is can we extend this to other scenarios past screening? In other words, can we use genotyping for women that already have abnormal Pap smears? I mean, I guess that would be the next transition for this, Tom, what do you think?

Dr. Wright:

Absolutely, Dr. Huh. Using extended genotypes, or genotyping, for that matter, for more than just screening is something that we've been talking about now ever since we got the first commercially available genotyping assay in the U.S. When you take ASCUS, for example, there are really two outcomes that you can do clinically. You can either send a woman to colposcopy, or you can put the woman into a follow-up at 12 months, if she's HPV positive. So, when we got the first data on genotyping in patients with ASCUS that was restricted to HPV 16 and 18. When we looked at the group of individuals who had other high-risk types, non-16, non-18, we found that the risk of those women having a high-grade lesion was high enough that most clinicians would want to send those patients on to immediate colposcopy. So when genotyping was restricted to only 16, 18, 45, we weren't able to identify a group of HPV-positive ASCUS patients with a low enough risk of having CIN 3 that we could tell them to simply come back in 12 months for repeat testing. Interestingly, though, now that we're getting data on more genotypes, we're beginning to see that there may be other options for identifying women at very low risk who have ASCUS and who are HPV positive, and those women may benefit from having simply follow-up at 12 months. Recently, Mark Schiffman, from the NCI, has looked at the high-grade cervical disease associated with different high-risk HPV genotypes in women with ASCUS from Kaiser Northern California. He found that more extended genotyping for types other than 16, 18, 45, really could be quite useful. I know you're very familiar with Dr. Schiffman's work, Dr. Huh. Could you describe his results in a little more depth?

Dr. Huh:

Yes, so a couple of things. Mark Schiffman, who works at the NCI, as you mentioned, worked with the Kaiser Permanente Northern California group where, at least for the United States, they probably have the most robust data prospectively regarding cervical cancer screening. So, a lot of what we propose or actually practice clinically is learned from that particular database, and I think for our audience and our listeners, for the most part, and there are some exceptions to this, that women that have this equivocal Pap ASCUS and they are high-risk HPV positive, the current recommendation for the majority of women, unless you are younger, is that you go to

colposcopy. And the problem is that a lot of that colposcopy may be completely unnecessary. So, is there a way to risk stratify women so that they don't need to go to colposcopy? Maybe they just need to come back in one year, as you mentioned, Dr. Wright. And that's kind of what Dr. Schiffman did in his paper in *Gynecologic Oncology* last year in September 2015. He used the dataset from Kaiser Permanente using a non-FDA-approved assay called Onclarity that's made by BD, and then basically did genotyping. And what he found is that, for instance, if you were 16 or type 18 or type 31 or type 33 HPV positive that those women definitely needed colposcopy because they had a much higher risk of having clinically significant disease, specifically, pre-invasive disease of the cervix and/or cervical cancer. But what they also found is that are other types that put the patients at much, much lower risk and, in reality, that those women didn't need colposcopy, and they could probably just be followed up with co-testing in one year, as you talked about earlier. So, what, in this strategy that he published, roughly about 40% of women wouldn't need colposcopy and they could be deferred to follow up a year later. Why is that clinically important? It's clinically important because it's really anxiety-provoking to tell women that all of a sudden they may have this abnormal Pap, they're going to need colposcopy, and they may need a biopsy, when, in fact, most of those women, over time, may completely resolve their HPV infection and their abnormal Pap, and be completely fine in one year. This isn't part of our clinical paradigm and algorithms today, but I do really fully suspect that it will become the paradigm and algorithm in the future because what we're learning more and more is that these other extended genotypes do play a clinical role. And so, it's both sides. I think we have a better idea of what women need colposcopy immediately, and as a consequence may need treatment, and what women can be followed. So what this allows us to do is improve the precision of our screening, and I think that's a huge advance. Our job, as clinicians, as you know Dr. Wright, is how do we translate that information effectively to providers and clinicians so that they're using the information correctly?

Dr. Wright:

Dr. Huh, you described the really important data that the NCI is bringing out of the Kaiser system on risk associated with different screening conditions. You described ASCUS and extended genotyping. I know they're looking at a variety of clinical situations in the Kaiser population. Some people have expressed concern, however, that Kaiser is a particularly low-risk population and that perhaps making guidance, based on Kaiser data, may put women in the general U.S. population at higher risk than we think. What are your thoughts on this?

Dr. Huh:

I think that is a very legitimate concern, Dr. Wright, and I think what we know from Dr. Schiffman's study, what he published is that the risk of CIN 3 or worse, in women who had ASCUS and were high-risk HPV positive, was about 5% and so there are other studies that have been published that indicate that that risk might be as high as 10%, double what's actually in the Kaiser Permanente Northern California group. And so, that raises a couple of concerns, one is this concept of generalizability. Can you take the data from Northern California Kaiser and extrapolate it to your local community or region? And that's been sort of the argument from many experts about whether or not we should rely on this one large dataset. And I think that, yes, that they probably have a lower risk population because they have been more intensively screened, and I'm not sure if you agree with this, Dr. Wright, but the majority of the country is actually at lower risk. So, in some ways, you can argue that maybe it is representative and generalizable. The other thing is that this is probably the best dataset that we have in the United States. Unfortunately, we don't have centralized registries like they do in Europe and Scandinavia; I wish that we did. But I would rather have more information than basically making screening guidelines or recommendations on no information. And the flipside concern is, well there's a risk of potentially over-screening, which for anyone that's in the screening world recognizes that that's been a growing concern, whether or not you're talking about cervical cancer or breast cancer. And so, yes, it's definitely lower and I think that people who are making policy changes or implementation changes for their region, their state, their community, they're going to need to take that into consideration. But, it's a guide, and I think that when we create algorithms we take that into consideration. We don't have a hard-fast one rule that's a one-size-fits-all for everybody. We can't do that because the United States is such a diverse population, but I think it is a concern. But I think that we have learned so much and I think we've made screening and practice, overall, much better, based on the Kaiser data.

Dr. Wright:

I think that's a really fair response and I completely agree with it. The only thing I would interject, additionally, is that I can't think of a biological reason why the relative risk of genotypes would be different from a low-risk population and a higher-risk population. So, even though Kaiser is well screened and relatively low risk, the relative risk that 16 versus 31 or 16 versus 33, I would think that relative risk

would be maintained across the different populations.

So Warner, is there any additional information you would like to share with our learners that you've not addressed during this discussion?

Dr. Huh:

Yes, I want to go back to an earlier point that you made about co-testing versus primary HPV screening. I mean, we're talking about the next wave of the value of HPV testing which is extended genotyping. But I think for the audience and listeners, I think it's important to recognize that we're learning more and more, almost on an exponential curve, about the simple value of using HPV testing as a screening modality. And I don't think that anyone would argue, we're not arguing, whether primary HPV is better than co-testing, but what we are arguing for is that you really should use HPV testing as a part of your backbone for screening, because what we know is that cytology or Pap smears alone are going to miss a lot of disease, but, and I just don't want to lose the simple message that HPV testing is really a better test when it comes to screening. What we're talking about today is sort of that building upon that central principle but, for the listeners, it's really important that you consider using HPV testing as an essential part of cervical cancer screening for women.

Dr. Wright:

I couldn't agree more. Even as a cytopathologist, I have to recognize that the days of using cytology alone for screening are probably coming to an end.

Dr. Huh:

I completely agree. So, Tom, let me ask you this, is there anything that you want to add that you'd like to share with our listeners or learners today that haven't been addressed in our conversation and discussion?

Dr. Wright:

I think the only thing that needs to be addressed is, as we extend beyond the simple HPV primary screening; if you're 16/18, you go to immediate colposcopy. HPV co-testing, if you've got a negative Pap, if you're 16/18 positive, we send you to immediate colposcopy. We're now starting to move beyond the simple message to something which is more complex and clinicians are going to have to know, is my patient 31 positive, is she 33 positive, does she have HPV 51? And as we move to this more complex world, we really are going to have to base management guidelines on risk assessment bands and how we do that is going to be still up for grabs, but we're all going to have to work together to keep extended genotyping simple enough so that clinicians, as you said earlier, Warner, there are a limited number of things you can do with an abnormal screening result and we need to be able to clearly know what a clinician does when they get a 31, a 33, a 51, etc.

Warner, we've come to the end of our discussion. Thanks for joining us via Skype. It's been a pleasure.

Dr. Huh:

Tom, thank you for having me; it's been really fun.

Dr. Wright:

I'm delighted. Take care.

Dr. Warner:

Thank you, Tom. It's been a pleasure.

Narrator:

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