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HPV Summit: Global Progress Towards Primary HPV Screening and its Impact on US Cervical Cancer Screening Policy

Narrator:
This is CME on ReachMD. This activity, HPV Summit: Global Progress Towards Primary HPV Screening and its Impact on US Cervical Cancer Screening Policy, is provided by Omnia Education and supported by an independent medical educational grant from Roche Diagnostics.

The experts of this discussion are: Dr. Thomas C. Wright, Jr., Professor Suzanne Garland, and Dr. Warner K. Huh.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives. Here is Dr. Thomas Wright.

Dr. Wright:
This is CME on ReachMD and I'm Dr. Thomas Wright. Today I'm speaking with Professor Suzanne Garland and Dr. Warner Huh. Welcome to the program, Professor Garland.

Professor Garland:
Thank you. Delighted to be here.

Dr. Wright:
And Dr. Huh?

Dr. Huh:
Thank you for having me, Dr. Wright. It's truly a pleasure.
Today we will have a wide-ranging conversation covering may different topics. We'll first talk about primary HPV screening, both in the United States as well as in Australia, and we'll have a conversation about the global impact. This conservation will also include age to start HPV primary screening, the interval of that screening, how to best incorporate genotyping into HPV primary screening, and lastly barriers to adoption both in the United States and globally. We also will address the potential impact of HPV vaccination on screening, and briefly touch upon the status of HPV vaccination in the United States, and also address how vaccination may impact our future screening efforts.

Dr. Wright:
The first question that I have for you, Dr. Huh, is that the U.S. screening guidelines have become so complicated recently, and I hear routinely from doctors, would HPV primary screening make it easier for them?

Dr. Huh:
Yes, that's a really good question, Dr. Wright, and you're right, it is confusing. And for the listeners, there are 3 screening options. We have Pap or cytology starting at 21, every 3 years. Or we have what's known as cotesting which is Pap plus cytology, starting at 30, every 5 years. And now we have HPV by itself starting at 25 years of age and that's every 3 years. So, how does one, as a provider or clinician, try to figure out how to screen? So, to answer your question, I do think it's going to get easier and actually kind of hot-off-the-

presses, the United States Preventative Services Task Force, which sets really many of our screening guidelines in the United States, just today actually, put draft recommendations that really greatly simplify screening, one of which is to, starting at 21 years of age, is to screen every 3 years with cytology, or just with HPV every 5 years. And I think you would agree, Dr. Wright, that's a pretty substantial leap from the current guidelines in that they also don't recommend cotesting.

Dr. Wright:
I agree totally, Warner. And the U.S. Preventative Services Task Force, I think, has taken a real step forward by making cytology or HPV primary screening, which is what most of the world has been doing. The United States is one of the only countries which has been doing cotesting in woman 30 years and older. Professor Garland, in Australia, how are you screening now?

Professor Garland:
Our government brought together an expert group to look at the evidence as to whether we should still be using Pap cytology as primary screening. This was called the Renewal Program. What I can tell you, to date, is that we were to move the primary HPV DNA screening with limited genotyping as from May of this year. However, this unfortunately was moved and we are now moving to this change in December of this year. This is all based on data from the U.S., from Europe, from the many studies where people have looked at the value of HPV DNA versus cytology, and we also looked at cotesting, and our learned group decided against cotesting. So, the plan in Australia is actually to start from 25, instead of 18, and to offer HPV DNA testing with 16 and 18 specifically being genotyped, and only to have reflex HPV if, and this is a rather complicated clinical algorithm which I can share with you, but basically if they are DNA negative on the testing, they go to 5-yearly HPV DNA testing only. If they are 16 or 18 positive, they go straight to colposcopic review. If they have high-risk HPV but not 16/18, then there is a reflex cytology through a liquid-based medium, and then the algorithm from there is dependent on whether it's low grade, in which case they have a repeat HPV DNA testing in 12 months with the same algorithm of care, and if, obviously, they have a high grade, they then again go to colposcopy.

Dr. Wright:
That algorithm, Professor Garland, is quite similar to what we have been using in the United States for HPV primary screening. I think one of the big differences is, in the U.S., we have said that if you are 16 or 18 positive, you don't need cytology.

About age-to-start HPV primary screening, previously in the United States, with the FDA approval, we were at 25 years and older. Do you still feel that's the right age, Dr. Huh?

Dr. Huh:
I think a couple of things that we've learned and one thing that we've learned, and a lot of this is based on the ATHENA trial which is by far the largest cervical cancer screening ever conducted, at least in the U.S. There's no question that when you look at that data, between 25 and 29 years of age, that we're missing cases of CIN 3 in women in that age bracket, if they're being screened with just cytology or Pap alone. But, in addition to that, many of those women who actually had CIN 3 had a completely normal Pap preceding their diagnosis. So, to answer your question simply, yes, I think screening at 25 with primary HPV is completely appropriate and reasonable, at least in the United States.

Dr. Wright:
Professor Garland, a number of European countries, who are adopting HPV primary screening, are doing a longer screening interval than every 5 years. Some are talking about every 7 years. Some are actually extending out to 10 years on their interval after they've had a couple of negative screens. What is the rationale in Australia for your interval?

Professor Garland:
I think we've really very much made a decision about what's safe, looking at the data that is there to date, and yes, we are using a 5-yearly interval, but again, I believe the data will be continually reviewed and modified as is required, particularly as the vaccinated cohort is going to become older and therefore impact on the CIN 3 changes.

Dr. Wright:
Dr. Huh, when we talk about managing HPV-positive women, one of the areas where there's been a lot of discussion is exactly which genotypes we should be most interested in. For the listeners, there are about 14 high-risk HPV genotypes and we currently call out, in the U.S., just 2 of them, 16 and 18. Dr. Huh, do you think we've selected the right ones?

Dr. Huh:
So, yes, you're right. So, our current screening and triage algorithm for primary HPV includes testing for multiple types of HPV. There are 14 high-risk types, but particularly parsing out 16 and 18. Why 16 and 18? Well, I think there are multiple data sets, including the ATHENA trial that demonstrate 16 and 18 are associated with a much higher risk of disease associated with those types. And so, particularly with 16, we get concerned about that because in women who are persistently infected with 16, there's no question that those

women are at a lifetime higher risk of developing CIN 3. There's some debate about 18, but what we know is that from some studies, that there's association with adenocarcinomas with type 18. Much, sort of later on, there's higher risk of disease, but in short, Dr. Wright, I think that we have picked 2 right types. I think what will be really interesting is, in due course, is whether we add more types to that to kind of further refine the triage.

Dr. Wright:
I agree with you.

Dr. Huh:
So, Dr. Wright, I'm just kind of curious, since you're a true leader in the area of primary HPV screening, but could you kind of just highlight or explain some of the data that supports the use of primary HPV screening, both in the U.S. and perhaps worldwide?

Dr. Wright:
There is a huge amount of data which clearly support the use of HPV primary screening. The first large trial was from Italy, and it was a randomized trial of a hundred thousand women, and these women were randomized to get either HPV alone or to get cytology alone. And the first finding of the trial was that they detected almost twice as many CIN 3's at baseline in the HPV arm as they did in the cytology arm. Twice as many. That is a huge increase. The second large finding of this trial was that they followed up the patients for up to 6 years. And these women had multiple additional screenings using cytology. At the end of the trial, the cytology arm never caught up with the HPV arm, despite multiple screenings with cytology. HPV always showed increased detection of high-grade disease. The other finding from this randomized clinical trial was that cervical cancer was actually reduced in the HPV arm, compared to the cytology arm. And I think as listeners think about this, it makes sense. If you have CIN 3 lesions, which go undetected, you follow them for 6 years, some of them will progress to an invasive cancer. So HPV actually gave better protection against invasive cancer than did multiple cytology screens. We have additional trials, randomized, controlled clinical trials, high-quality data from the Netherlands, from Sweden, and from the U.K., and they all showed the same result: increased detection of high-grade disease with HPV compared to cytology, and less development of high-grade disease over time in HPV-negative women compared to HPV-positive women.

Dr. Huh:
So, Tom, in light of that, do you want to just briefly comment on what are the relevant studies pertinent to North America or the United States for our listeners?

Dr. Wright:
One of the big reasons, I think, that the U.S. Preventative Services Task Force, prior to today, did not adopt HPV primary screening, was that we had relatively limited data from North America. We had 1 randomized trial from Canada that enrolled 5000 women, and that trial showed that HPV alone had increased detection of high-grade disease, compared to cytology alone. What we got though, in the last several years, is a prospective data coming out of ATHENA. ATHENA enrolled over 40,000 women, and every woman got a gynecological exam, they had an HPV test, they had liquid-based cytology, and women who were positive on either the liquid-based cytology or the HPV test underwent colposcopy. And we found that the sensitivity of HPV, in the ATHENA trial, at baseline, was almost twice that of liquid-based cytology. HPV detected 100% of the CIN 3 lesions at baseline. Cytology detected about 54 or 55% of the high-grade lesions. So, HPV gave a clear advantage to the detection of CIN 3. There also was a 3-year followup component of ATHENA. And what we found during the followup was more high-grade disease was detected in women who were Pap-negative at baseline, compared to women who were HPV-negative at baseline. This means that screening with HPV over a 3-year interval, gives you better protection against developing high-grade disease over the next 3 years, than does a negative cytology.

Dr. Wright:
Dr. Huh, what do you perceive to be the barriers to the introduction of primary HPV screening in the United States?

Dr. Huh:
There are actually several. First and foremost one of the greatest barriers is just education and understanding. I mean, Tom, you know that, you wrote the original interim guidance on cotesting back in 2004 and 2005, and it's taken us well over a decade for people to truly embrace cotesting. And so part of it is education. The other part is that because, until just now, that there was sort of a disparity in screening recommendations. In other words, we wrote an interim guidance paper looking at primary HPV and its pros and cons and values and potential concerns, yet it hadn't been really investigated by the task force. It's challenging for providers to have patients who are on different types of insurances, commercial insurance, governmental insurance, Medicaid, and you want one cohesive sort of plan and policy, one that's consistent so that you can screen people the same way, every single time. And I think that's why the task force draft recommendations today is really important, because it provides us with some of that consistency. I think the third thing is that, you know, I think people are now just starting to embrace cotesting and now we're telling them, "Well, get rid of the Pap." And so, I think that there is some controversy about whether the Pap adds or does not add value above and beyond HPV testing. And so, again, I think it all

comes down to education, but first and foremost, I think, going back to your original question to me, providers want, sort of simplification of screening. And the task force guidelines take a massive leap in that direction.

Dr. Wright:
Professor Garland, how have you addressed these barriers now that you're facing imminent introduction of HPV primary screening in Australia?

Professor Garland:
I would concur with Dr. Huh, that yes, education, education, education is really fundamental to the success of this program. And the education really needs to be at all levels. It needs to go to the lay public, to women, to clinicians. And we're only just starting to see the colleges embrace this and take that on. One of the things I say to clinicians is that the Pap test has stood the test of time, but remember, Dr. Papanicolaou described this back in 1928. So, we have a much more sensitive test now and we need to get on and change over to that, particularly with the changes made by the high coverage of vaccination and consequent reduction in Pap abnormalities. Really, the positive predictive value of the Pap cytology falls for the detection of these lesions with the reduction in numbers. Another thing I think that's really important is that we've tried to simplify our clinical algorithm of care with the Renewal Program. So, there was a lot of discussion initially. Should you have a different algorithm for those who are vaccinated and non-vaccinated? The agreement was to have the same program for everyone, and I think that's appropriate. I think another challenge that's worth highlighting is that just as the cytology program, we need to have a good quality assurance/quality control for HPV DNA testing.

Dr. Wright:
That's very useful, Professor Garland.
For those of you tuning in you're listening to CME on ReachMD. I'm Thomas Wright, and together I have Professor Garland and Dr. Warner Huh, and we are discussing HPV primary screening and HPV vaccination.

Dr. Huh, if you can, summarize the impact of HPV vaccination.

Dr. Huh:
Yes, I'll comment on what the impact is at least in the United States. So, what we know is, and interestingly, this report just came out recently, Tom, that based on the 2016 National U.S. Teen Immunization Survey, so roughly 45% of teens are getting the full series for HPV vaccination, and roughly about 60% are getting at least 1 shot of the HPV vaccine. Lauri Markowitz, and others, who published a paper several years back, looked at the impact in terms of HPV prevalence, at least in the United States, and what they saw was anywhere between basically a 55 to 70% drop in the decrease of 16 and 18, the types related to the vaccine.

Dr. Wright:
I agree. But now that we're up to about 60% of teens getting at least 1 dose of HPV vaccine, is that going to impact the U.S. screening recommendations?

Dr. Huh:
I think it's the golden question, Tom. And so, in 2017, and maybe for the next several years, probably not. I don't think it's going to have an impact, but in the next 10 years, absolutely. I very much envision, in the United States, where women who have been vaccinated and we can document this, that they should be screened in a very different manner than women who have not been vaccinated.

Professor Garland:
So, Dr. Wright, can you explain to us how vaccination against HPV is going to impact the performance of cytology in the U.S.?

Dr. Wright:
There's been a lot of discussion that there's going to be a differential impact of HPV vaccination on the performance of cytology. And I think the concerns come from 2 factors. The first is, we already know that cytology only detects 50 to 60% of high-grade lesions, and a considerable portion of those it detects are associated with HPV 16. Now, we know that the lesions which do not get detected with cytology tend to shed fewer cells. So, it's not that cytology couldn't detect them, it's just that when the cytotechs review the slides, there are only a few cells so they miss the abnormal cells. Since HPV 16-associated lesions are larger, we expect that they exfoliate more cells and, therefore, they're easier to detect when the cytotechnologist screens the slide. What will happen when we differentially get rid of HPV 16, and we have lesions caused by HPV 31 and 33 and 39, they're going to be harder for cytology to detect. So, we think, over time, in a vaccinated population, cytology will perform less well. The other problem with cytology in a vaccinated population, and I've certainly heard from cytologists in Australia that they are seeing this problem, is that as a person screens Pap smears, the majority of them are normal. So they tend to get very complacent looking at the slides, because only about 1 in 20 is going to have a real abnormal lesion. If you take that to 1 in 40 or 1 in 50, it's going to be much harder for the cytotechnologist to maintain the level of vigilance when they're screening, to pick up the actual abnormal cases.

Professor Garland:
Thank you, Tom. That's exactly what we feel too.

Dr. Huh:
But don't you think that same phenomenon is going to occur with HPV testing?

Dr. Wright:
I don't. And that's because the HPV test is a different type test than cytology. The HPV tests all test for 13 or 14 high-risk types of HPV. And they have been clinically validated to actually have cutoffs for each of those HPV types which is associated with disease. So, the cutoff for HPV 16 is different than the cutoff for HPV 31 or 33. So they should perform exactly the same as they do today when you have lesions which are associated, predominantly, with non-16 and 18 genotypes. So, I think it will continue to perform quite well.

Professor Garland:
So, Dr. Wright, can you describe the uptake in primary screening globally, please?

Dr. Wright:
Clearly, Australia has adopted it, as you've already very nicely discussed during this discussion. We've also seen the U.K. decide to go to HPV primary screening. The Netherlands is adopting it. Sweden is adopting it. Turkey, of all countries, has decided to adopt HPV primary screening and it is implemented there. We also are seeing very large pilot programs going on in Latin America. Mexico's got a large pilot program as does Argentina, and they fully plan to adopt HPV primary screening at the end of their pilot programs. I was recently in China and they're talking about their pilot program for HPV primary screening. They're going to enroll 500,000 women in their pilot program, and if it goes successfully they are going to adopt HPV primary screening. So, I think we are right at the point where lots of countries are going to adopt it. And as we heard today, the United States now, with the most recent draft guidance from the U.S. Preventative Services Task Force, has decided that HPV primary screening is a strategy for use in our country.

Dr. Wright:
Professor Garland, Dr. Huh, this has been a great discussion today. I really want to thank you for joining and helping our listeners at CME on ReachMD. Thank you.

Professor Garland:
Thank you for having me onboard.

Dr. Huh:
Thank you for having us, Tom. It was a great conversation.
I think it's important for the listeners to recognize that there has been some substantial progress and changes in the area of cervical cancer screening. Most particularly, the impact and the importance of HPV primary screening, particularly as we vaccinate more and more women in the world, as well as the United States. What we recognize is that cytology does fall short in terms of missing disease as a screening mechanism, and that basically all of the scientific literature in the last ten years, have demonstrated improved sensitivity and detection of disease with primary HPV screening. But, most importantly, the fact that we can safely extend screening intervals by using this strategy. So, in the years to come it makes perfect sense that the U.S. and world-wide adopt this, and it's important for our listeners and for providers to understand that although cytology did its job, and did its job effectively 50 years ago in reducing the morbidity and mortality of cervical cancer, we have to look for it in terms of looking at replacements for screening, and it appears that primary HPV screening is that best option.

Narrator:
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