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High-Risk HPV Primary Testing for Cervical Cancer: A Case Presentation

Narrator:

Welcome to CME on ReachMD. This segment, “High Risk HPV Primary Testing for Cervical Cancer: A Case Presentation”, is sponsored by Omnia Education.

Your faculty joining us today is Dr. Warner Huh, the Margaret Cameron Spain Endowed Chair in Obstetrics and Gynecology, Professor and Division Director of Obstetrics and Gynecology at the University of Alabama at Birmingham, in Birmingham, Alabama.

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While the prevalence of cervical cancer in the population has decreased over the years, there are still 12,820 new cases and 4,120 deaths estimated in 2017; however, despite this progress, there is marked uncertainty among healthcare providers regarding the optimal screening strategy for cervical cancer. While both primary high-risk HPV testing and cotesting approaches are known to be superior to cytology-alone, current evidence suggests that patients as well as providers continue to favor cytology-based testing annually. Healthcare providers thus face challenges in integrating cotesting and primary high-risk HPV testing in clinical practice, or choosing one over the other for individual patients. The case presented in this CME activity addresses some of the issues faced by clinicians when selecting cervical cancer screening strategies for their patients.

Dr. Huh:
Hello, everyone. My name is Warner Huh. I am a Division Director and Professor in Gynecologic Oncology at the University of Alabama at Birmingham in Birmingham, Alabama. I am happy to discuss a case presentation on the use of high-risk HPV primary testing for cervical cancer.

So, as a matter of my disclosure, I have served as a nonpaid consultant to Roche Molecular Systems, specifically in relationship to their ATHENA trial, which I’ll talk about in a second, and also sit on the Scientific Advisory Board specific to publications for Merck Vaccines for their V503 platform, also known as Gardasil 9.

So, three main objectives associated with this learning effort, and one of which is to understand the underlying data supporting the FDA decision on high-risk HPV primary testing for cervical cancer screening and then to better understand its relationship to current harmonized guidelines, also to identify and evaluate adoption barriers to high-risk HPV primary testing for cervical cancer in medical practice, and then, lastly, more effectively counsel and educate patients regarding the risk of HPV infection and the sequential approach taken to manage that very specific risk.

I want to start off this with a basic case presentation, one in which I think a lot of primary providers and OB/GYNs see in 2017. This is a 36-year-old, healthy woman. She has a history of normal cervical cancer screening, but her last Pap smear was about 4 years ago. She comes back to your office for resumption of her cervical cancer screening as well as her just general women’s health maintenance, and you ultimately elect to use a primary HPV test alone to screen her.

Some basic questions I think that we'll address in this presentation but also that are commonly asked and are important, one of which is: Compared to cytology, also known as a Pap smear alone, is primary HPV more sensitive or less sensitive? B) How is the specimen collected in the office? In other words, is it a blood test? Is it a Pap test? Is it collected from saliva or from some other bodily fluid? And then, lastly, what test would you use to screen this patient in this setting?

The human papilloma virus, also known as HPV, is an important virus because what we know since the 1990s that this is a causative link to cervical cancer. In essence, the vast overwhelming majority of invasive cervical cancer in the United States, as well as worldwide, is associated with high-risk HPV. Almost virtually all of preinvasive lesions, specifically CIN 3, are also associated with HPV as well. In the United States as well as worldwide, there are 13 or 14 high-risk genotypes that are specifically associated with cervical cancer in preinvasive lesions, and when we say high risk, they're high risk from the perspective that they are associated with an increased risk of developing cervical cancer, and it's these types specifically that we test in conjunction with cervical cancer screening.

The ATHENA study, which was conducted in the United States, is an FDA registration study. This is by far the largest US screening study ever conducted in the setting of cervical cancer screening, included a cohort of over 42,000 women. All these women were 25 years or older in the US undergoing routine screening. They underwent a routine gynecologic exam, underwent a ThinPrep liquid-based cytology test, had HPV testing as well as genotyping. I'll talk about genotyping in further detail in a second. And all women that were HPV positive and/or had an abnormal Pap underwent colposcopy, but more importantly, there was a subset of women who were HPV negative, or normal, who also underwent colposcopy as well, and we do this just to kind of understand the baseline level of disease.

Again, this is one of the most well-controlled designed studies in this setting, and again, it was an FDA registration study, and we've learned a tremendous amount from this large study in terms of screening performance, what may or may not be a better screening test, how things like HPV testing including genotyping work in this particular population.

One thing that we have recognized over the last maybe 15 years or so is that there is a significant amount of variability when it comes to cervical cytology or Pap smears, and what we know—and this actually dates back to an original study from Dr. Nanda known as the Duke Report back in 2000 -- is that the sensitivity or, in essence, a reflection of the false negative rate of cytology is actually quite poor. And so in the ATHENA study, there was actually 4 labs that did the Pap test, and the sensitivity ranges anywhere from 40% to as high as 75%, so what that translates for the audience is a false negative rate of anywhere from 25% to roughly 60%, so a lot of variability. And so we also determined the variability by looking at the ASCUS rate. ASCUS basically stands for atypical squamous cells of undetermined significance. It is, in essence, an equivocal Pap smear. The cytology lab is unable to tell you whether or not it's definitively normal or abnormal. And what you can see here is the rate actually varies significantly as well from 3.8% to almost 10%. So this is pretty dramatic, and so we know this from the ATHENA trial, but we've seen this as well from many studies across the United States as well as worldwide.

What I think was interesting is that in this study over half of the women who had a bona fide precancerous lesion of the cervix actually had preceding, normal, liquid-based Pap or cytology results. And this is one of the reasons why we're doing this learning module is because it highlights the limitation of cytology or Pap smears and the fact that we are likely missing a significant amount of disease in our screened population.

Similarly, when you look at the sensitivity of an HPV test compared to the sensitivity of cytology, what we recognize is the sensitivity is much, much better than cytology. It's not even subtle. So, when you look at the four same labs that did cytology or a Pap test and look at their HPV sensitivity, the sensitivity is usually in the 90% range, meaning that the false negative rate is about 10%. It's probably even lower than that when you even look at other larger studies, but recognize that the sensitivity differential is pretty dramatic and that we're probably missing a lot less disease screening with HPV testing compared to cytology or Pap testing alone.

On a much broader scale, when you look at the comparative sensitivities across multiple cross-sectional studies -- some of these studies were done in Europe; some obviously we've included the ATHENA trial at the bottom -- but when you look at actually the far right column, on the second of the far right column, Pap tests and HPV, what you can see from these studies is really the significant difference between Pap cytology and HPV testing in terms of the sensitivity. I'll give you a classic example. Dr. Mayrand in 2007 published one of the very first randomized trials in this setting in the New England Journal of Medicine, included over 10,000 women, and what you can see is a significant difference, 58% for Pap sensitivity and 83% for HPV, and across the board you will unilaterally see much better sensitivity with HPV compared to Pap. And so, universally speaking, there is a basically global acceptance that the sensitivity of HPV is much greater than the sensitivity of cytology. And based on my review of the literature and talking about this topic multiple times, I don't think there's a single paper out there that demonstrates that the sensitivity of cytology by itself is better than the sensitivity of HPV. And I think this is really important because I feel that most providers are going to really want to be able to tell their patients after a screening test that if their test is normal, they want to be able to tell the patient, "Yes, your test is definitively normal." My concern in 2017 is that we are not able to do that reproducibly, as well as reliably, based on Pap smears or cytology, and I think that's

the major barrier behind this process.

So, exactly what is primary HPV screening? Well, primary HPV screening is now an FDA-approved strategy. It utilizes a test called the Cobas 4800 test, and it basically is a PCR-based test that looks at 14 different types of HPV. There are two specific types that we're concerned about, type 16 and type 18. I'll talk to you why that these are important specifically. And, basically, we're using the HPV test first and in some circumstances using cytology or Pap smear as what we call the reflex. So, there was a lot of criticism initially when this got approved that Pap smears were going away. They're not going away. I would argue that we're just using Pap smears in a much better strategic manner than we're using it presently.

As a follow-up to this case presentation, let's say that her testing comes back as negative for high-risk HPV, including negative for type 16 and type 18. What do you recommend now, and when should she return? Well, when you look at the algorithm again, if you happen to be negative for all HPV types, they should go back to routine screening. Well, based on this algorithm, the routine screening is actually at 3 years, mainly because all this data is based on the ATHENA trial, and there was only really 3 years of follow-up on the ATHENA trial, and so we really can't go past 3 years, but what we're recommending is that women come back in 3 years to be rescreened if they happen to be HPV negative. Could the interval be extended? Yes, it definitely could be. We don't have prospective data to indicate that that's safe, but there's multiple worldwide data indicating that you probably could extend that interval well out to 5 years or perhaps even longer. I think the most important thing for the audience to recognize is that when you have a negative HPV result, that's highly compelling evidence that your risk for developing cervical cancer over the next 3 years plus is incredibly small. You cannot say that with a Pap smear.

So, why are 16 and 18 particularly important? Well, 16 and 18 are particularly important because these happen to be the two most common types that are associated with squamous cell carcinomas as well as adenocarcinomas of the cervix. So, what you can see here is in blue is type 16, green is the other types, but again, 16 and 18 are really key components to the development of squamous cell carcinomas and adenocarcinomas. So, approximately 70 to 75% of cervical cancers in the US are attributable just to these two types. It's one of the reasons why the quadrivalent vaccine, bivalent vaccine and now the nonavalent vaccine have 16 and 18, because they are major key HPV types in terms of its relationship to cervical cancer. One quick note, and I'll talk about this in a second, is type 18 is very important, particularly for adenocarcinomas of the cervix.

So, when you look at the risk over at least a 15-year period, particularly in a screened population—and this is a paper that Dr. Mark Schiffman from the NCI, who is an extraordinarily well-known expert in this area, published back in 2011 from the Kaiser Portland cohort—what you can see is when you look at 15 years of follow-up here, that there is an incremental rise in terms of the risk of and the detection of CIN 3 in these patients. That risk, as you can see, is much greater than the other types that are related to HPV and certainly much greater, as you can see on the black dotted line at the bottom, for those women who happen to be HPV negative. What you see is a slower rise related to HPV 18 in green, and I'm going to talk shortly about why that's really relevant in this learning module.

When you actually look at the prevalence, so how much HPV is out there, for 16 and 18 the prevalence drops from 30 to 39 years of age when you go into the next subsequent deciles of age and subsequently largely flatten out, but the combined prevalence for type 16 and 18 was 1.5% overall. The reason this is important is I don't want people in the audience to think that 16 and 18 prevalence is widely common in this screened population. It actually isn't, and it does drop with time, but the detection of 16 and 18 are important risk factors in terms of the development of cervical cancer and cervical precancer.

As a follow-up, so if her testing returned as high-risk HPV positive and then positive for type 18 but negative for type 16, how would you proceed at this point, and then why is type 18 positivity important in this setting? Well, as I mentioned, the reason it's important is that if you're type 18 positive, we know that more of those are associated potentially with adenocarcinomas of the cervix. Adenocarcinomas of the cervix are typically higher up in the cervix, often Pap smears fail to pick those up, and so this is why HPV testing is important, because we recognize that the sensitivity is even more limited in the detection of adenocarcinomas. And there are some in the community, in the professional community as well, that are concerned that adenocarcinomas have maybe a worse prognosis because they're picked up at a later stage but mainly because they're harder to detect. The important thing here is you'll see a lag, so in the green line the detection of CIN 3 related to 18 occurs later, at 5 to 10 years of follow-up or 10 to 15 years of follow-up, and much of that may be because it's, again, like I said, it's just harder to get to those lesions because they reside higher up the endocervical canal. So, how would you manage this patient? Well, you would manage this patient by proceeding straight to colposcopy in a woman who is type 18 positive. It's the exact same in the woman who happened to be type 16 positive.

So, the last part of the case presentation, if her testing returned as high-risk HPV positive but negative for 16 and 18, you know, how, again, would you proceed with this? Well, if you look at the screening algorithm here, here is where we use cytology. And so we want you to use a Pap smear, and if the Pap smear comes back normal, you follow up in 12 months. If the Pap smear comes back as ASCUS or worse, you go to colposcopy. And so, and this is the way we should think about this. So, most screening tests, you always

use the most sensitive test first and then confirm those results with a more specific test. In many ways we've been doing it backwards in cervical cancer screening. In essence what we're doing here is basically re-correcting the order. HPV testing is more sensitive. It's the better test upfront. And you confirm those findings by using the more specific test, which in this case would be cytology. So, again, cytology or Pap smears is not going away. We're just using it more logically in this manner.

So, the approval for this occurred back in 2014. A couple things that I want the audience to be recognized, one is that it's just for one test. And I know that creates some consternation for our providers because their labs may not use a cobas test. There is an emerging body of evidence with other tests, but right now there's only one FDA-approved test. Interestingly, the approval starts at 25 years of age for this type of screening. And what we know is that if you look at women between 25 and 29 years of age, almost, as I mentioned earlier, almost 60% of those women who had CIN 3 or precancer actually had an entirely normal Pap smear before that diagnosis. We talked about the very specific management algorithm that is being carried out with primary HPV screening, as I've demonstrated multiple times, and, again, the guidance has been developed by SGO as well as the ASCCP for the use of primary HPV screening, and we did this to basically guide clinicians so they can further understand how to appropriately use this type of testing.

We published these guidelines in January 2015, and they are published in the Obstetrics and Gynecology journal as well as the Journal of Lower Genital Tract Disease, and, again, primary HPV screening should not begin before 25 years of age, so use it from 25 years onwards with a 3-year interval and which was considered to be a reasonable screening approach. And, again, it's considered to be--the algorithm is considered to be--a reasonable approach for managing women who happen to be HPV positive.

It also recommends following these guidelines if you're going to use primary HPV screening. And, again, it also adds that you stop at 65 years of age if they have a negative history, if you didn't have a hysterectomy, and follow up with co-testing at 12 months if you happen to be HPV positive and cytology 16 and 18 negative. And you should only use an FDA-approved test. This is really important. And, again, I think there's a growing body of evidence in terms of looking at other assays that might be appropriate for the use of primary HPV screening.

A couple things I just want to spend some time on, one of which is there are a lot of questions about barriers in terms of how to use this. Yes, we published a guidance document on this. The United States Preventive Services Task Force is actively looking at primary HPV screening. We hope to have their recommendations announced and published soon, maybe later this year, perhaps, but this is something that the task force is actively looking at as well. I know it's confusing for providers because we have three separate screening options at this point, but I think the important thing to recognize is that there is an overwhelming large body of evidence that dictates that and dictates and shows that HPV testing is a better screening test than Pap smears alone.

I think the more important issue is how do you educate and counsel not just providers but patients on how to use this? Well, I think, like I mentioned earlier, it's a better test, it has a lower false negative rate, and we need to tell patients that. And so, patients and our providers should have a certain level of reassurance. When they get screened and they are told that they have a normal test, they want to feel good about that test. The other problem is that as we vaccinate more and more women in this country, we know the prevalence of disease is going to drop. It's going to be harder and harder to screen these women, and so now is the time to make sure that we embrace the right or better test so we can adequately screen women and certainly not miss disease in this setting.

But anyway, I want to thank the audience for your time and listening to this learning module, and it's been an honor, and thank you very much.

Narrator:
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