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Transforming Cervical Cancer Screening and Management: New Guidelines, New Tests
A Case-Based Discussion

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Transforming Cervical Cancer Screening and Management: New Guidelines, New Tests : A Case-Based Discussion” is provided by Omnia Education.

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Dr. Huh:
So I recently encountered a patient in my clinical practice, a 40-year-old, healthy, G3, P2 patient with a history of normal cytology over her lifetime, but also never underwent HPV testing, and undergoes recent primary HPV screening. And she’s noted to be high-risk HPV positive, but is negative for type 16 and 18. The question I have is, what triage strategies should be considered in this setting?

And so this is CME on ReachMD, and my name is Dr. Warner Huh.

Dr. Cantrell:
And I’m Dr. Leigh Cantrell.

Dr. Stoler:
And I’m Dr. Mark Stoler.

Dr. Huh:
So I think this case really highlights some really important points about where we are with cervical cancer screening. And beginning with you, Dr. Stoler, I thought maybe we could talk about what this means.

Dr. Stoler:
Well, the issue of what does it mean to be HPV positive and then specifically for a genotype that’s not 16/18. Really, many people know that 99.7% of all cervical cancers are due to high-risk HPV, particularly squamous cell carcinomas are due to high-risk HPV DNA at a very high level, and 70% of the squamous cancers are due to HPV 16 and 18. If you look at adenocarcinomas, which make up, about 15%-20% of the cancers in the screened population, 16 and 18 and type 45 account for almost 95% of carcinomas.

And as you alluded to in the history, this woman was screened primarily with cytology. In the United States today, we still have 3 different screening systems, if you will. Many patients, particularly those in the underserved populations, still get cervical cytology and we know, of course, that Pap smear cytology is responsible for a 70%-90% reduction in cervical cancer prevalence over the last 30 or 40 years, but as we screen more and more, it becomes harder and harder to detect the less obvious cancers, and that cytology now is under some criticism because it’s not sensitive for the carcinomas and the precancers that we need to find to prevent the development of cancer. Because of this, over 20 years ago we started introducing in the US the concept of co-testing, and I would say most patients who were insured or have good medical care in the US are getting co-testing, meaning they’re getting a Pap and a clinically validated

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HPV test.

Some tests give you genotypic information, like 16 and 18; others do not. Since 2014, we've also had primary HPV testing available in the US, and while this has been available for over 8 years in the US as an FDA-approved algorithm that's progressively but rather slowly being adopted in the US, in the rest of the world, where co-testing really never took hold, many countries – England, Australia, Canada, many European countries, and Scandinavia – have skipped the co-testing step. They've gone right to primary HPV testing. And the reason for that is that if I had to show you one image regarding the comparison between cytology and co-testing, it would be the study from Ronco where they pull results of 4 large, randomized, controlled trials, involving almost 175,000 women. And what these show is that cytology is substantially less sensitive than HPV testing – something we've known for a very long time. In fact, over 8 years, primary HPV testing will add 60%-70% protection relative to cytology, in terms of cancer detection, meaning if you get tested with a primary HPV test, you're going to find that cancer earlier and not have it develop over time, because the cancer or the precancer that will lead to that cancer is going to be detected and eradicated.

Dr. Huh:
So, Dr. Cantrell, I thought maybe you might want to comment on the various societies that have cervical cancer screening recommendations, and maybe some of the differences as well.

Dr. Cantrell:
There are different guidelines. There's the American Cancer Society [ACS], the American Society for Colposcopy and Cervical Pathology [ASCCP], the American College of OB-GYN, the US Preventive Task Force Guidelines – and all of those are slightly different. We've all decided that starting to screen at age 21, maybe adding HPV at 25, but there are differences between these that are nuanced. The American Cancer Society's are the only ones that currently say that HPV screening should be the primary screening method and should start at 25 and proceed to age 65. I think for practitioners, who may even be oncologists, it can be confusing to know what is the best thing to do for their patients. And we know that there's been an increased incidence in women who are younger, in their early 30s, that are starting to have more cervical cancers. And I think that those trends are concerning. They pick a recommendation to follow, and then it can be difficult for them.

Dr. Huh:
No, I totally agree. And I think one of the challenges that we face, particularly in the United States, despite the science and despite the progress of our understanding of the natural history of cervical cancer and its precursors, is that clinicians are, really, still pretty unclear and inconsistent on how to use these guidelines and how to best incorporate them into their clinical practice. At least in the US, we have a long, long way to go.

Dr. Stoler:
So, Warner, I'd like to make a comment, if I could.

Dr. Huh:
Sure.

Dr. Stoler:
So as Leigh was mentioning, the incidence of cancer in younger women in their 30s seems to be increasing, particularly in the last few years when nobody was being screened, and it's in those women, the recent data from, for instance, the ATHENA trial and the other HPV validation trials have shown that, surprisingly, in younger women, cytology doesn't perform as well as we expected, and so the added sensitivity of HPV is critical in that young age group, just like it is in older women, to finding the precancers that we need to eradicate.

Dr. Huh:
I think that's an excellent point.

So one of the things that I want to get into, and that, again, I'll have you comment on this further, Dr. Cantrell, is about the ACS guidelines and how they're uniquely different. And I know that you mentioned about primary HPV testing, and so for the listeners, I thought it might be helpful about what exactly that means. So when we say primary HPV screening or testing, for you to comment on exactly what that means as it stands today.

Dr. Cantrell:
It's not available everywhere in the United States currently. And that means that the only screening test that a woman gets is HPV and if she has HPV present, and if there's any type, what the type is. And the ASC guidelines recommend that that start at age 25 and continue on to age 65. There are other options for locations that don't have primary HPV testing. And that would be to do a Pap every 3 years or a Pap and HPV co-testing every 5 years.

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And so I think because it is not equivalent across the country, it makes it very difficult for practitioners to know exactly what to do, and for some of them, HPV testing alone is just not an option.

Dr. Huh:
So, Dr. Stoler, I know you're highly familiar with the ATHENA trial. I thought you might want to comment on how the ATHENA trial formed our current understanding of the value of primary HPV screening.

Dr. Stoler:
Well, ATHENA was the registration for the FDA registration trial for the cobas® HPV test, which is 1 of 2 – it's a moving target. There are now 2 FDA-approved tests for primary HPV screening. But ATHENA was for the cobas® test, and what we learned in ATHENA, a very large trial of over 40,000 individuals, is how much better primary HPV is than cytology alone and even co-testing, which it's statistically indistinguishable from co-testing. So the ACS guideline in 2020, which Leigh alluded to, caused a lot of consternation, not because they recommended primary HPV as the preferred method going forward, but they also gave a warning, which was very unusual in a guideline document, to say, well, the next iteration of these guidelines, which will come out in the next couple of years, there aren't going to be these other options. We want people to do primary HPV because we think the data is overwhelmingly in favor of doing this as the best medicine for women. Now, those issues that Leigh mentioned, namely, the availability of primary HPV, not every clinician knows which HPV test their lab does, and only 2 of the 4 currently available tests are approved for primary HPV screening. And so, yeah, we have a lot of transitioning to do to, in essence, follow what's going on in a lot of countries outside of the US, who have also come to the same conclusion as the American Cancer Society.

Dr. Huh:
You hit on a great point, Dr. Stoler, which is that I was quite surprised at how kind of stern the recommendation was in the American Cancer Society guidelines and that in the past, our guidelines have generally been inclusive of multiple different options, being cognizant that not all labs, clinics, health systems were able to accommodate modern types of screening. But like you said, the data is so compelling and so overwhelming that they're essentially doubling down on this, and they're basically going with the science, like you said, like, not just in the US It's also consistent with many parts of the world.

Dr. Stoler:
The other point is that this shouldn't come as a surprise. So the ACS published the guideline in 2012, which was 2 years before the FDA approval, even though ATHENA was mostly done and analyzed. And it's this problem of guidelines not being able to reference things that aren't published. If you read that very long document in 2012 – all these guidelines are kind of long – you see that they're already saying we think primary HPV is going to be the way to go. It just wasn't FDA-approved and generally available. So it's not a surprise if you've followed this – not everybody follows these things, day in, day out like we do, but this is a process that's 10 years old and continuing to evolve.

Dr. Huh:
Yeah, you're spot on.

For those tuning in, you're listening to CME on ReachMD. My name is Dr. Huh, and I'm here today with Dr. Stoler and Dr. Cantrell, and we're just about to dive deeper into the cervical cancer screening guidelines and distill this into truly practical, clinical pearls for our audience.

So on the topic of guidelines – the screening guidelines – going outside of the American Cancer Society screening guidelines, we fully anticipate that the United States Preventive Services Task Force will be updating and releasing their guidelines in the near future. So I'm going to go to you, Dr. Cantrell. What do you think that this will ultimately mean to providers, when they do release their guidelines?

Dr. Cantrell:
You know, I think we are all anticipating that they will shift, just like the American Cancer Society guidelines, and be primarily HPV-based for screening, and I think we all have realized that that is the best way to determine a patient's risk of developing cancer and, of course, that's what we're trying to avoid.

Dr. Huh:
Dr. Stoler made a comment earlier about the 2012 guidelines, but I think the best part about the 2012 screening guidelines, from at least the Task Force, as well as American Cancer Society, is there was this incredible harmonization between the guidelines, that they were, for the most part, extremely consistent with one another, and we didn't have this confusion about whose guidelines to use. Now, we live in a world where ACS says one thing, and the Task Force says another thing.

Dr. Cantrell:
Right.

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Dr. Huh:
Do you guys feel that we'll return to that level of harmonization when the Task Force comes out with their recommendations?

Dr. Cantrell:
I certainly hope so. I think for providers it's really confusing, and even more so for their patients. No one wants their patient to get cancer, and they only want to provide the best care. And so I think really understanding how primary HPV-based screening is better than Pap smears alone or co-testing is really important, and that if people can understand that and then explain it to their patients, I think it would just be so nice for everything to be in harmony.

Dr. Huh:
My question is about the harmonization and the fact that will we get to a point that they'll be harmonized again.

Dr. Cantrell:
We certainly hope that the guidelines will be harmonized, because for providers to know how best to screen their patient and to be able to explain to patients that all the societies agree that this is the best way to screen is certainly much easier for everyone to understand, and it just seems that the data is pointing to risk-based screening with HPV testing alone.

Dr. Huh:
Dr. Stoler, your thoughts?

Dr. Stoler:
Well, first of all, I'm all in favor of harmonization. And it should come to pass, I would hope, because we're all operating off the same, today, incredible databases where we have, 2, 3, 4 trials with hundreds of thousands of individuals.

I mean we're talking levels of evidence that never existed before, when we used to make recommendations about annual Paps, which was good for its time, but obviously, over-screening led to some harm. The so I think harmonization will come to pass, and people should realize that there's an incredible amount of work that goes into these guideline processes and that the decision process, at least for the American Cancer Society, where I've been most closely involved, is really driven by what is the best balance between the good of screening versus the harms of screening, and that drives the guideline.

Dr. Huh:
I think you guys make great, salient points on this topic, and the one thing I will say is I still think there's a fair percentage of women in this country that are still getting annual Pap smears. And I think when the recommendations come out, we'll be stepping even further away from, A, doing annual cytology but, B, just doing cytology in general. And like you both have mentioned, that the data is so compelling, but I think for our listeners, I think it's important for them to understand that cytology is just clearly an inferior test compared to HPV testing in this day and age, and there's very little reason why you should be using cytology to screen your patients at this point.

The other thing I want to just talk about, and I know our listeners have this question, is how do we manage women that have a positive HPV test? And how do we manage women that have specific genotyping, like type 16, type 18, type 45? And the ASCCP back in 2019 published its basically management of abnormalities guidelines, which is really a risk-based assessment. And so for those of our listeners that are familiar with our previous ASCCP guidelines, they were very much algorithmically driven, so you had a result and you went down the algorithm and you saw the recommendation. Now our recommendations are based on a calculation of risk, and that risk then dictates that you do really 1 of 5 things. We've kept it very simple: 1 is treatment, 2 is colpo, 3 is come back in 1 year, come back in 3 years, or come back in 5 years. And that's all distilled based on a calculated risk on the combination of their testing results and often their biopsy results. And so for our audience, just to recognize that the management schema is very, very different than it was over the last 15-plus years. It also allows us to add new tests, like extended genotyping, genotyping beyond 16, type 18, and type 45, and the question I'm about to ask Dr. Stoler about the value of dual staining and how we plug that into the algorithms. So I think for our listeners, it's really important to understand, like, how you utilize this information, and there is a resource that allows you to figure out how to best triage these patients that have a positive HPV test.

And so, to that point, Dr. Stoler, I thought maybe you might want to talk about what dual staining is, how it fits in primary HPV screening, and better yet, maybe to use this case study that I discussed in the very beginning as an example.

Dr. Stoler:
Lets's go back to when we're talking about primary HPV. We know from these big trials that in the United States today, if you screen with a clinically valid primary HPV test, every place will be a little different. But let's say 10%-15% of women will be positive. We can't take all those women to colpo, because only 1% of women screened with a positive test have CIN 3 or cancer. So we need to triage those patients, and in the current guideline, the triage test is cytology. If you have a type other than 16 or 18, you use cytology. If the cytology is abnormal at any level, you take the patient to colposcopy. We take everybody with 16 and 18 to colpo because their risk – for

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instance in the ATHENA trial, one of the remarkable results that Dr. Huh published was that a woman 27 years old with a normal Pap smear, who would have been told, oh, you're normal, you're fine – if they're HPV-16 positive, they have a 10% cross-sectional risk of having CIN 3 and a 25% risk in 3 years. So it's those kinds of data that force the need for triage, and just like we think primary HPV is a better triage, we now have very large data, including FDA approvals, that show that there's a better triage test than cytology, just like a primary HPV is better than cytology than screening tests, extended genotyping and dual stain are better than cytology for the triage test by a significant amount.

So how does that work? Well, dual stain refers to using immunohistochemistry on the cytology slide – on a liquid-based cytology slide, to look for 2 markers that by themselves are never co-expressed unless you have neoplastically transformed cells. So if one cell on these slides, in an HPV-positive woman, is dual-stain positive, that's sufficient to say she has a very significant risk for having a high-grade lesion on colposcopy; she needs to go to colposcopy.

Extended genotyping speaks to the fact – and again, this has been recently FDA-approved as well – that we now know that the 12 other genotypes aren't equal in their risk profiles. There's some that are so rare – still, they cause a tiny fraction of cancers, but it's so rare that you can put those patients into the 1-year or 3-year follow-up category, whereas other types, the ASCCP guidelines really talk about the concept of equal management for equal risk. So if type 31, for instance, or type 33 have risk profiles that are the same or greater than HPV 18 – which happens to be what the data show – well, if you're taking 18 to colposcopy, why wouldn't you take 31 and 33 to colposcopy?

So we look at the example, the case study that Warner presented. In the beginning, the woman has had all these normal Pap smears, but now has had an HPV test, and it's not 16 or 18. Currently, we have 3 strategies. We can do a cytology and look and see if it's abnormal, and if it's abnormal, take her to colposcopy, and if it's normal, bring her back in 1 year.

We can do extended genotyping, if our test allows for extended genotyping, as 1 of the 2 FDA-approved examples does. And depending upon the type, you may cross those various thresholds of colpo, 3-year or 1-year, 3-year, or 5-year returns, and mostly 1-year return. Or you can do dual stain, where we know that the positive predictive value of dual stain is so high – approximately 25% more sensitive than cytology in this situation. That can raise your risk to the level of, certainly, colpo referral if it's positive and potentially even to the consideration, if the risk is above 25%, then considering therapy, depending upon how the patient might be followed up. So the final point would be that we have now data-driven decisions available to us that stratify risk in a way that is superior for the HPV-positive woman compared to cytology alone, and so I think you're going to see an evolution of the triage guidelines, just like the screening guidelines.

Dr. Huh:
I think that's a great response, and again, this is about optimizing disease detection at the end of the day. I'm glad you brought up the whole concept of equal management for equal risk as it relates to the guidelines, because this is another example of how that concept can be played out clinically and be of value to the provider.

Well, anyway, this has been a truly fascinating discussion, but before we wrap up, Dr. Cantrell and Dr. Stoler, do you have 1 take-home message that you'd like to share with our audience? And before I ask you, I'll just share mine, and I'll go first. I guess my take home message for the audience is to recognize the value of a negative HPV test, and I think we talked a lot about positives – I'm going to let Dr. Cantrell and Dr. Stoler do that, maybe – but the negative test is so powerfully important for women, and I think that we would all agree that we would love to be able to tell a woman that they have a negative test, and that is truly predictive of a very small risk of developing a cervical cancer precursor and even for cervical cancer. And in my opinion, that's exactly what a negative HPV test provides.

So I'll go to you, Dr. Cantrell, next. If you could just kind of share your take-home message for the audience.

Dr. Cantrell:
I train residents and do board exams, and across the country, people are struggling with what do we do? And I think I would just encourage people to stay up to date with understanding what it means to do primary HPV screening and what dual staining is going to mean and to really understand it so that they can offer it to their patients because it just offers such a better and more precise way to prevent cancers. And that's what we all want to do and to catch things before they turn into a cancer. I think that's what's exciting about the future. I think we're going to just be in a much better place a few years from now.

Dr. Huh:
Dr. Stoler?

Dr. Stoler:
Well, part of my take-home message that bears reemphasizing was part of Dr. Huh's. If you're going to have a woman and you're going

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to screen her, let's screen her with the most data-driven optimal test we know of, and a negative HPV is significantly more reassuring than a negative Pap smear. If you're HPV-positive, you're the 10%-15% of women who are HPV-positive, risk stratification is the name of the game in all of these guidelines, and now we have biologically based, marker-driven risk stratification that in substantial clinical trials has been shown to be superior to morphology alone in calculating that risk.

Dr. Huh:
I love both your responses. They're spot on and so accurate. But unfortunately, that's all the time that we have today, and so I want to thank our audience for listening in, and obviously thank you, Dr. Cantrell and Dr. Stoler, for joining me today and for sharing all of your valuable insights and expertise on this topic. It was fantastic speaking with the both of you today.

Dr. Cantrell:
Thanks, Warner.

Dr. Stoler:
Yes, thanks, Warner. It was a pleasure, as always.

Announcer:
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