Transcript Details

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Consensus Recommendations for Use of p16/Ki-67 Dual Staining Cytology in the Management of Individuals Testing Positive for HPV

Announcer:
Welcome to CME on ReachMD. This activity, titled “Consensus Recommendations for Use of p16/Ki-67 Dual Staining Cytology in the Management of Individuals Testing Positive for HPV” is provided by Omnia Education.

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Dr. Huh:
Effective triage tests are needed to help decide which patients should go on more diagnostic testing for cervical cancer and which can be just followed. The focus of our discussion today is the rationale for including p16/Ki-67 dual-standing cytology, and we're going to be calling this “dual stain” throughout the podcast, into the management of patients who test positive for HPV.

This is CME on ReachMD, and my name is Dr. Warner Huh.

Dr. Levinson:
And I'm Dr. Kimberly Levinson.

Dr. Huh:
So, Kim, maybe you can explain to our listeners is exactly what is p16 and Ki-67 dual staining and maybe the history behind that.

Dr. Levinson:
So we'll start out talking about dual staining and exactly what's being measured. So dual staining measures both p16 and Ki-67. And p16 is a cyclin-dependent kinase inhibitor, which acts as a tumor suppressor. And we know that p16 is upregulated in the presence of active HPV infection. Ki-67 is a proliferation marker and it's actually a nuclear antigen stain. That is detected in cells that are in the non-G0 phase of the cell cycle. So this really marks cells that are undergoing replication, and we know that when those 2 stains are seen together, that really is a marker of the presence of not only HPV but active HPV infection.

Dr. Huh:
And so, Kim, just to kind of clarify again, this is irrespective of the type of HPV and really kind of all HPV infection; is that correct?

Dr. Levinson:
Yeah, that's exactly right. And so for this, it really helps us to understand better when HPV is present, if it's acting on those cells to cause both proliferation and abnormality in the cells that can lead to cervical cancers, which is why this stain is so helpful.

Dr. Huh:
So the next question to you, which is if you could explain sort of the lead up to the publication for the recent 2024 recommendations for dual staining using p16 and Ki-67 on cytology and the management of HPV-positive individuals. What are we testing for exactly, and what's the aim here?

Dr. Levinson:
Yeah, absolutely. So as most of us know, Pap smear testing was really the first truly valuable cervical cancer screening test. And that was introduced in the 1930s. And throughout the second half of the 1900s, this really decreased the incidence of cervical cancer. But we know that this screening strategy has a pretty low sensitivity rate and a high false positive rate. So in the early 2000s, cotesting with both Pap smear testing and HPV testing was introduced, and this afforded us a much higher negative predictive value for screening. And so that also afforded us longer screening intervals.

And then finally, HPV testing alone was approved by the FDA in 2014 and was added to guidelines in 2018. And currently the American Cancer Society [ACS] recommends this as the preferred screening strategy for women 26 to 65 years old. So this test actually has the advantage of being much more sensitive than the Pap smear screening test and also much less subjective. And in fact, randomized controlled trials have shown that when we compare HPV testing alone to Pap smear testing, the detection for predicting cervical cancer is increased by about 60% to 70%. And so data suggest that this really is the best screening strategy for prevention of cervical cancer. The other thing that I think is important is that in 2019, the ASCCP [American Society for Colposcopy and Cervical Pathology] guidelines transitioned to a risk-based model. And so with that risk-based model, instead of deciding who needs colposcopy based on a result, we are looking at the risk for cervical high-grade dysplasia.

So I wonder if we can take this discussion a little bit further, Warner, and talk about what gaps there are in the current cervical cancer screening triage area and how this dual stain plays a role in that.

Dr. Huh:
Yeah, and before I get into that, Kim, to the points that you were making, the addition of dual staining builds upon this concept of risk-based management, and that risk-based management sort of paradigm was kind of put into play by ASCCP, the NCI [National Cancer Institute], and others back in 2019. This just builds upon that platform. And we talk a lot about risk and wanted the listeners to understand what we mean by risk and why that's so important here.

But to address your specific question about gaps, we obviously have 3 primary modalities for screening. One is cytology or Pap by itself, which for over 50 years markedly reduced the incidence in mortality of cervical cancer. But the problem with Pap alone is that it has a relatively low sensitivity, meaning that the false negative rate is relatively high. And the only way for cytology to be effective as a screening test is you've got to repeat it frequently. And so if you have patients who don't come in every 5 to 10 years, cytology fails those patients and fails as a screening paradigm.

And then the second one that you mentioned, which came into play in the 2000s was cotesting, which is the combination of both cytology or Pap and HPV testing. And that HPV testing has morphed into what we call panel testing to genotype testing, and we'll get into that in a second. And cotesting has been effective. But the third strategy is HPV testing by itself, also known as HPV primary testing. And what we know is that, probably, cotesting, in reality, doesn't add that much above and beyond HPV testing by itself. And when you combine those 2 tests, HPV testing is probably the more powerful test of the 2.

The problem with HPV testing is that it has a lower specificity but a higher sensitivity, which then in turn can lead to a higher number of colposcopies, biopsies, and procedures and particularly in younger women. The other issue also is that when you develop an abnormality and you combine it with HPV, it's still a little bit unclear which women really benefit from further evaluation like a colposcopy. And that's exactly why dual staining with p16 and Ki-67 is so important.

I know our listeners are like, look at, wow, we have all these tests just for screening, but think about it this way: Dual staining provides you with a much greater level of precision and understanding of which woman or which patient actually needs further evaluation, versus which women or patient needs actually to be followed over time. So it's a long answer to your question, Kim, but I think dual staining is a paradigm-shifting test that allows us a lot more precision and specificity.

So for those just tuning in, you're listening to ReachMD, I'm Dr. Warner Huh. And here with me today is Dr. Kimberly Levinson. We're just about to delve further into the rationale for including p16 and Ki67 dual standing cytology in the management of patients that test positive for HPV.

Kim, let me ask you this question: How does the utility of p16/Ki-67 dual-staining cytology now fit into our daily practice? I know that you're going to talk about the recent recommendations, but maybe if you could go over the more salient recommendations.

Dr. Levinson:
So this kind of gets into the nitty gritty of what do these recommendations tell us and how do we utilize this dual stain? And so the first part of this is for exactly what we were just talking about. The patients who get primary HPV testing who then become positive – and we don't have any other results that are telling us or guiding us which of these patients actually need to undergo colposcopy. And so these

guidelines help us in that way by telling us, utilizing another test, so the dual-staining test to identify risk of either it being positive and thus those women need to go on to get a colposcopy, or being negative, and those women then can repeat testing in 1 year. So this is really the functionality of the test is risk-stratifying women with HPV-positive primary HPV testing to either going directly to colposcopy or returning in a year for another test. So that's the first recommendation there.

The second recommendation talks about patients who also underwent primary HPV testing but then had further genotype testing. So the genotype testing, as you mentioned, really delineates the patients with the higher-risk types. So HPV 16 and 18 versus the other 12 high-risk types which can cause cervical cancers but do so less frequently than 16 and 18.

So for those patients who have undergone high-risk HPV testing and then have also been genotyped for type 16 and 18, we have further delineation of what to do for these patients based on dual-staining testing. So for patients who are HPV 16 positive or HPV 18 positive, we know that with dual staining positive or negative, it really does further delineate their risk. But because we're looking at trying to determine further, we want to be very careful about making sure that we capture all the patients who need colposcopy, all of those patients will undergo colposcopy at this time. For those patients who are HPV positive but are not 16 or 18 positive, so they have 1 of the other 12 high-risk types, those patients can be further delineated out by the dual-stain test, either going to colposcopy due to a positive test or returning in a year for a negative test. So this really allows us further delineation of risk based on the dual-staining test. And we have a lot of studies that have shown us that this really helps us to delineate the risk for high-grade cervical dysplasia in the future.

Dr. Huh:
Yeah, there's a lot to unpack there, and you did a great job. I have just 2 things to add. One of which is think about dual stain as a way to better triage your patients who are HPV positive. But I think the important thing in general is that if your patients are type 16 and 18 positive, those patients really still need to undergo colposcopy. What we're trying to really better delineate is the management strategy for all those other women, as you mentioned. And the last thing is that much of this will be incorporated in the app that ASCCP creates. And again, it's built on that platform of risk-based guidelines. And so hopefully this will not be too complicated and the general practitioner and provider for screening and management abnormalities will understand how to incorporate this.

Dr. Levinson:
Yeah, I think that what you said is exactly right, thinking about how to better delineate those women who we don't really know what their risk is. We know 16 and 18 have an elevated risk, and that's why, being very careful, we want to make sure that those women undergo colposcopy and that we capture anything there that could lead to high-grade dysplasia. But the other 12 types, we still are in a little bit of a bind of in terms of who really needs colposcopy or not. And I think that this is really helping to identify the risk for women who are either HPV positive without genotyping or who have one of these other high-risk types that's not type 16 or 18.

Dr. Huh:
Yeah, totally agree. Kim, before we wrap up today, what's your one take-home message for our audience today?

Dr. Levinson:
So my one take-home, I think, is that the good news is that we have testing that improves our sensitivity and specificity for detecting cervical precancer lesions. And I think this is a really important advancement in our understanding of how we can prevent cervical cancer. So utilizing these tests to really risk-stratify in patient populations is going to be tremendously beneficial. And I think as we continue to move forward, our ability to utilize better tests is really critical.

How about for you, Warner?

Dr. Huh:
Yeah, I mean, my take-home message for this group is to understand that dual staining with p16 and Ki-67 is an FDA-approved test. And a lot of this is done by the lab, right? So our providers and clinicians out there that are doing the screening and the testing may not exactly know what assay is being used or which HPV test is being used. And so what I would encourage our audience and listeners to think about is you may want to inquire to your lab whether this dual-staining platform is available to them, and if it is, great, understanding how you incorporate that into your practice. And if not, why not? And you may want to ask that question because I do believe that this is paradigm changing in terms of how we manage these abnormalities.

Well, unfortunately that's all the time that we have today so I want to thank our audience for listening in and thank you again, Dr. Kimberly Levinson, for sharing your expertise and insight. It's always great speaking with you and I really appreciate your time.

Dr. Levinson:
Yeah, this has been a wonderful conversation, Warner, and I really appreciate having this conversation about these new guidelines and

look forward to talking with you soon again.

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