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### Addressing Unmet Needs in Triage Options During Cervical Cancer Screening

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Addressing Unmet Needs in Triage Options During Cervical Cancer Screening" is provided by Omnia Education and is supported by an independent educational grant from Roche Diagnostics.

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Dr. Cohen:

Regardless of which screening approach you use, effective triage tests are needed to decide which patients will go on to more diagnostic testing and which can be just followed. Unfortunately, current diagnostic uncertainty leads to confusion in triage and clouds patient management. This will be the focus of our discussion today. Welcome to CME on ReachMD. I'm Dr. Steven Cohen, and joining me today is Dr. Thomas Wright, Professor Emeritus of Pathology and Cell Biology at Columbia University in New York. Welcome to the program, Tom.

Dr. Wright:

Thank you for having me on today, Dr. Cohen.

Dr. Cohen:

To start off, Tom, when thinking about how we approach cervical cancer screening, what is some of the current unmet needs with regard to this triage?

Dr. Wright:

Back when cytology was first introduced, we did not have very sensitive cytology, and it tended to call women either negative or positive. But then we got ASCUS with the Bethesda system, and that ended up with considerable numbers of women at low risk of disease needing some form of triage. We then have moved on now to HPV for primary screening and for co-testing, and that makes a problem much worse. So, we've got large numbers of women in whom we just don't know whether the positive screening test is meaningful or not.

Dr. Cohen:

So now that we have that background, Tom, what options exist to remove the diagnostic uncertainty that currently exists in triage?

Dr. Wright:

One of the most interesting options for triage is the use of p16. p16 is a cell cycle regulatory protein, which is normally expressed in very low levels in cervical cells. However, when a transforming HPV infection takes place, p16 gets overexpressed to the point that we can detect it using immunohistochemical methods. What this does is allow me to look at cervical biopsy, and if I'm concerned it could be a high-grade lesion, I use p16 staining, and if it stains positively, I call it a CIN2 or CIN3. There've been large trials which have been used to get FDA approval of p16 for immunohistochemistry on histology. The trial was the CERTAIN trial. It took a large number of cervical biopsies and 70 pathologists, and what it did was compare the sensitivity and the specificity of the diagnosis made by the surgical pathologist versus a diagnosis made by a panel of expert pathologists. When the cervical pathologists looked at only the H&E slide or

looked at the H&E slide together with a p16 slide, when the pathologist used both H&E and the p16 slide, their overall sensitivity for CIN2 or greater increased by 11.5%. The increase in sensitivity, which was seen, was accompanied not by a decrease in specificity, but also by a 3% increase in specificity. So overall diagnostic accuracy improves when the surgical pathologist had access to p16 immunostaining.

Now that is, with respect, the histology. Cytology is slightly different. In histology, we have architecture. In cytology, I do not have the histology. Therefore, we have to add another biomarker. And the biomarker that we use is Ki-67. This is a marker of cells which are proliferating. So when I see cells on cytology which are positive for both p16 and Ki-67, so they're dual-stained positive, I know that we have a transforming HPV infection, and I know that woman is at high risk for having a high-grade lesion. Dual staining is now FDA approved in the United States. It's called CINtec PLUS Pap, and it's by the same company that got the FDA approval for histology for p16.

Dr. Cohen:

For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Steven Cohen, and today, I'm speaking with Dr. Thomas Wright about reducing the diagnostic uncertainty that currently exists within our triage options during cervical cancer screening.

Now, Tom, before getting into a deeper discussion of how p16 and Ki-67 dual-staining cytology can be used as part of triage, could you describe how they actually work and what data exists to validate the potential of this within the clinical patient population?

Dr. Wright:

One was a trial I was involved with, which was the ATHENA trial. And what we found in ATHENA was that the women who were HPV positive with a negative cytology had almost twice the risk of having CIN3 identified over a three-year period of time than women who were HPV positive who were dual-stained negative. In addition, the sensitivity of cytology for identifying a CIN3 over a three-year period of time in HPV positive women was only 52%, whereas the sensitivity of dual stain was 75%. In the ATHENA trial, specificity really was almost equivalent for the two methodologies. We also looked at the use of dual stain for triage of women who were 12 other HPV positive. Those are women who don't have HPV 16 or 18. And again, there, we found that the sensitivity of cytology was lower than the sensitivity of dual stain, but the specificity was equivalent.

The very recent large data set from Kaiser Northern California from Wentzensen also shows real importance of using dual staining to determine how you manage an HPV-positive woman. They took over 3,000 HPV-positive women, who they followed in the Kaiser system for up to three years. They did both cytology, if they were HPV positive, as well as dual staining. And what they found was that dual staining showed a better risk stratification for CIN3 or greater than did cytology. Dual-staining positive women had a 12% risk of CIN3+ over the three-year period, whereas those women who were cytology positive, only had a 10% risk. Now that doesn't sound like a huge difference, but when you put it over a very large population of women, it does make a big difference. In addition, they found that women who were HPV 16, 18 negative and who were also dual-stained negative, had a risk that was low enough for them to go into extended screening. Overall, in the Kaiser experience, triage of HPV-positive women using dual staining would reduce colposcopies by about a third.

Dr. Cohen:

Now, let's explore how p16 and Ki-67 dual-staining cytology might be utilized for primary HPV testing alone and also in the co-testing realm.

Dr. Wright:

Now we have an animation, which will describe those triage approaches, which I would like to share with everybody.

Dr. Wright:

Now that we have seen the animation, I'd like to go into it in a little more depth to put some clinical context into it. First, for HPV primary screening. If a woman is positive for the 12 other genotypes, what we recommend is that we use dual staining as opposed to cytology to determine which women need colposcopy. If one of these women is dual-stained positive, we'll send her on to colpo. If she's dual-stained negative, we'll follow her up in 12 months. Now all of the women who are 16, 18 positive are going on to colposcopy. But there is a real benefit to doing dual staining even in women who have 16 and 18 because that tells the colposcopist which women are at greatest risk for having high-grade lesions. So the use of dual stain lets the clinician modify their treatment so that they are sure they're focusing on the highest-risk women. Co-testing their HPV-positive women, who are negative cytology, would have both 16 and 18 genotyping and dual staining, and this gives us very nice risk stratification. Those women with 12 other HPV, who are dual-stained positive, are at high risk even though they have a known cytology. They need colposcopy. Similarly, those who are dual-stained negative, they can get followed up in 12 months just like we do with primary screening. It is also worthwhile, though, to do dual staining on those women who've got 16 or 18 because if those women, just like in primary screening, are dual-stained positive, they are at higher risk, and they can then have their management modified slightly.

Dr. Cohen:

Unfortunately, we are almost at the end of today's program, but before we go, could you share some final thoughts and messages to the audience?

Dr. Wright:

I only have a very brief final thought, which is now that we've got very sensitive screening methods, the big hurdle in front of us is to figure out how to triage HPV-positive women so that women who are at low risk can get sent to routine screening and those who are at highest risk can get colposcopy and workup. And this is going to require new and sensitive triage approaches, and dual staining looks like it has the potential to be that.

Dr. Cohen:

It's a great way to round out today's discussion on how we can potentially address some of the current unmet needs in triage during cervical cancer screening. And I'd like to thank my guest, Dr. Thomas Wright, for joining me today in this discussion. It was great seeing you and speaking with you again today, Tom.

Dr. Wright:

Same to you, Steve.

Announcer:

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