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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Riding the Wave of Change in Cervical Cancer Screening: Managing Patients in Light of Risk Using Extended Genotyping

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Riding the Wave of Change in Cervical Cancer Screening: Managing Patients in Light of Risk Using Extended Genotyping” is provided by Omnia Education.

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Dr. Shulman:
Today’s topic is once again front and center as we look to address unmet needs associated with cervical cancer screening and review recent guideline updates that may impact your clinical practice.

This is CME on ReachMD, and I’m Dr. Lee Shulman.

Dr. Moscicki:
And I’m Barbara Moscicki.

Dr. Shulman:
In 2020, as COVID-19 dominated the news and many elective procedures were put on hold, it’s very possible that healthcare providers missed out on clinically valuable information. Of particular note is the issuance of new cervical cancer screening guidelines by both the American Cancer Society [ACS] and the American Society for Colposcopy and Cervical Pathology [ASCCP]. Dr. Moscicki, could you provide your thoughts on the ACS guideline updates and the likely impact on clinical practice?

Dr. Moscicki:
So the ACS made some really brave choices. They made 2 that are quite distinct from our current screening practices in that currently we start with cytology at the age of 21 years, and at the age of 30, we switch over from cytology at every-3-year intervals to co-testing, that is, cytology with HPV testing. So some of the data now really show how co-testing is a little bit of a waste of performing cytology if you do it initially. And the reason is, is that primary HPV screening is a very powerful tool that is very sensitive to pick up CIN3 and cervical cancers, whereas we know cytology is not quite as sensitive. So the ACS came out with ”a preferred recommendation that we use primary HPV testing, that is, using HPV testing alone. And there currently are 2 FDA-approved tests, the Roche Cobas and the BD Onclarity. And this is very important to understand that it must be an FDA-approved test according to the ACS screening guidelines. The other thing about primary HPV is not only is it a very sensitive test, but it has an incredible negative predictive value. That is, if you are negative for a high-risk HPV test, the likelihood of anything happening in the next 5 years is very low. So we can increase those intervals, as well – like cytology we use every 3 years. Primary HPV testing, we can use every 5 years. The other bold piece I think ACS did is they started screening at the age of 25 years instead of 21 years. Why is that? Well, first of all, using HPV testing in a 24-year-old is not a good idea because there’s a lot of HPV and there’s very little cervical cancer, and also, low rates of even CIN3+, which is what we try to pick up in our cervical cancer screening.

So, that’s a very important piece, that over 50% of the target population here in the US – 11- to 12-year-olds – have now at least

received 1 HPV vaccine, and they're reaching this age of cervical cancer screening. So cytology even works worse among HPV-vaccinated cohorts because you're getting rid of those villains, HPV 16 and 18 and other high-risk types. So these are basically some of the really good things about the 2020 cervical cancer screening guidelines.

I think it's also important to talk about discontinuation. We want to, again, know that we're going to stop at women of age of 65 years, but with 2 caveats. No history of a prior CIN grade 2 or more severe within the past 25 years, and they must have a documented, adequate negative prior screening in the 10-year period before turning age 65. So with these, we're hoping that we're going to become a lot more cost-effective in our screening.

But that brings me to the second part of the question – looking at the ASCCP 2020 guidelines and how that's going to also do the management of an abnormal test. Because now our primary test for cervical cancer screening is HPV. So what we know about it, I just told you the positives, right? Great negative predictive value, very sensitive. But it has what we call a very low positive predictive value, that is, you're going to have a lot of women who are going to be HPV positive who do not have any underlying disease. So what's important about that is that the ASCCP has come up with what we call risk-based management guidelines on that positive test. And those differences have to do with whether that woman, in whatever triage test you decide you're going to use, they would go straight to colposcopy. Another caveat may be that they have a test result that says, "Oh, well, you're not really low risk, but I need to see you back sooner, but I don't need to send you off to colposcopy." So that woman may come back in a year. And we have another set of scenarios where you say, "Oh, my gosh. This triage test says something is super wrong, and you need to get treatment almost right away." And of course, the fourth scenario is the triage test says, "Eh, you don't have to worry about anything. You can come back in 5 years."

Dr. Shulman:
Dr. Moscicki, could you please discuss newer approaches to screening and triage that have been approved in the United States? I'm thinking in particular about primary HPV screening and the p16/Ki-67 dual staining.

Dr. Moscicki:
This is actually key to understanding how primary HPV testing is going to work now and in the future. So there's a low positive predictive value of HPV testing, so having some type of triage is necessary for cost-effective triage, specifically here in the United States. There are 3 approved – one is cytology as a triage. So if you're high-risk HPV positive, and you have ASC-US or greater, it is recommended that you go off to colposcopy. If you have genotyping, and that's getting a 16 or 18 test, that is enough to send you off to colposcopy, because a risk of having a 16, 18 positive test moves you to that risk of CIN3 is great enough that you need to go immediately to colposcopy.

So a newer test that's hit the market is something called, "dual staining." And that was also recently FDA-approved, and there are 2 markers, Ki-67 and p16, and it's when a cell actually stains for both of those markers. That is basically indicative of cell cycle deregulation, which is the hallmark for a transforming HPV infection. So in that scenario, if you are high-risk HPV positive, and you are dual-stain positive, it recommends you go off to colposcopy. What we think is going to be more powerful, though, is the combination of genotyping and the other high-risk positive. That is a scenario where a woman's genotype – 16, 18 – you go off to colposcopy. If you are positive for the other high-risk, non-16/18 type, then dual stain could also be used as a triage: positive, you go to colposcopy. If you are dual-stain negative, you can come back in 12 months. Whereas in cytology, that same scenario would leave you, if you were 16, 18 positive, and as I mentioned, other high risk, they were cytology negative, follow up in 12 months. If you're cytology positive, you would go off to colposcopy. So that's a combination of both currently how we use genotyping – that specifically, 16 and 18 – and where we would use either cytology or dual stain to further triage women who are the non-16/18 – the other high-risk positive types.

Dr. Shulman:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Barbara Moscicki. We're just about to discuss cervical cancer testing and how to conduct risk-based management.

Dr. Moscicki:
So, Dr. Shulman, can you quickly review the currently available FDA-approved tests that I just alluded to and describe their role also in the risk-based management?

Dr. Shulman:
If you consider the available testing for evaluating cervical cancer risk or cervical dysplasia risk, there are really 3 main types. The first is cytology. There is not an FDA-cleared cytology test. It's pathology assessment performed by a cytopathologist, and it examines the cells in a sample taken from the cervix. So there is no FDA-approved cytology-alone, assay. Where we get into FDA approval are those that incorporate the use of HPV evaluation. And the first set of tests to do this were the co-testing algorithms. And these approvals go back to the late 2000s, early 2010s. And these are tests that combine cytology to actually still look at the cells as well as

testing for HPV DNA in the same sample. Now, some of these co-testing assays look at specific HPV types, what we would call genotyping, and some of them do not. Some of them just basically say, yes, high-risk HPV, no high-risk HPV.

So again, the ones that look at high-risk HPV, they all assess for HPV type 16 and 18, as Barbara alluded. These are the HPV types that provide the greatest concern for us as clinicians about progression to severe dysplasia and potentially to malignancy. But there are 2 of these assays – co-test assays – the Aptima HPV 16 and 18/45, as well as the most recently, Onclarity HPV – that look at other high-risk HPV types in addition to 16 and 18.

Most recently, the primary HPV test to evaluate the DNA of oncogenic or high-risk types of HPV in a sample taken from the cervix. And there are 2 such FDA-approved tests. The first was the Cobas HPV, which essentially looks for HPV types 16 and 18 as well as grouping the others into high-risk types into a detection group. And the more recent assessment is the Onclarity HPV, which again provides a more detailed overview of the HPV types, 16 and 18, as well as the other high-risk HPV types.

Clearly the ability to utilize the knowledge of high-risk HPV in a particular sample provides a far superior approach to determining whether or not that particular woman is more likely to progress to a more serious cervical issue of dysplasia or even malignancy, or whether she is likely not going to proceed to a serious clinical outcome and therefore there is no need to increase the frequency of surveillance. This has been a profound improvement over what we had used from really the beginning of cervical cancer screening with cytology.

Dr. Moscicki:
And I would like to make one other point about the powerful tool that primary HPV testing has brought to the table. And that is, if you have a known negative result and 5 years later you come in with a positive test, your risk is very different than if you come in with no known prior history of screening. It makes a difference between requiring referral to colposcopy to where you can have surveillance, especially if that type is non-16/18. This is not true of cytology. It does not give us the same incredible, powerful information about a woman's risk that primary HPV testing does. So that's one more cost-effective great opportunity that we have using primary HPV testing.

Dr. Shulman:
Barbara, can you describe the clinical implication of the extended genotype?

Dr. Moscicki:
Women who are positive for 16 or 18 – they're at unusual risk; they require immediate attention. On the other hand, we have these "other high-risk types" that we throw into a bucket. Well, there's been some really interesting information that's come out, basically from the National Cancer Institute's research group, working in collaboration with other folks within the Northern California Kaiser Permanente. And they've nicely shown that not all non-16/18 high-risk types behave the same. There are types, such as 33, 31, 35, 52, that definitely have a lower risk than 16 or 18, but they have a much higher risk than these other types, such as 58 or 66 or 51. Therefore, if we can start teasing out the differences between those moderate risk versus what we call high risk, but have a really low risk, and they almost behave as some of the ones that are HPV negative, that is one more cost-effective measure that we can take. So I do think it's going to be – stay tuned – that we soon will have these extended genotypings in our algorithms for management as well.

Dr. Shulman:
You are so correct, that those other 12 viral types are not equal. There are those that are more equal than others, and there are those that really do require our attention, and these newer algorithms, these newer tests, this more comprehensive genomic assessment, are likely going to lead to even better outcomes than we've seen with the earlier assays.

Barbara, can you share your one take-home message with our audience?

Dr. Moscicki:
The first one is we need to ensure that women get cervical cancer screening tests. Whether it is cytology, whether it's co-testing, or whether it's primary HPV, the number one is working with your local laboratory but making sure that women do not fall off schedule, as women were not coming in during COVID, and that has drastic consequences for women's health. And my second is to remember that primary HPV screening is a cervical cancer screening test and that's how the FDA approved it. It is not an STD check. So when women start asking you, "Where did this come from?" we need to help them understand, this is a cervical cancer screening test and this is how this test was developed.

Dr. Shulman:
Unfortunately, that is all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Moscicki, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Moscicki:
And it was great being here, and I really appreciate your comments for the rights of women. Thank you.

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