Transcript Details
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Exploring New Frontiers in Cervical Cancer Screening

Announcer Introduction:
You're listening to *Advances in Women's Health* on ReachMD, and this episode is sponsored by Roche Diagnostics. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to *Advances in Women's Health* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss some of the latest advancements in cervical cancer screening is Dr. Diane Harper. Dr. Harper is a Professor in the Department of Family Medicine and Obstetrics and Gynecology at the University of Michigan. Dr. Harper, thank you so much for being here today.

Dr. Harper:
Thank you.

Dr. Caudle:
So, Dr. Harper, just to give us a frame of reference, what's currently recommended in the clinical guidelines for cervical cancer screening?

Dr. Harper:
Cervical cancer is important to eliminate. We're on the cusp of being able to do that with HPV vaccines and with the new strategies that we have for cervical cancer screening. Right now, we have at least three different bodies that are recommending different screening strategies for cervical cancer screening. The American Cancer Society's recommendations are primary HPV testing. The American College of Obstetrics and Gynecology also recommends primary HPV testing but still is recommending co-testing with that. Co-testing means that you do both cytology and HPV testing at the same time for the woman when she is there for her visit. The United States Preventive Services Task Force has looked at the evidence of the different methods of screening for cervical cancer and has shown that the benefits of primary HPV testing outweigh the harms associated with co-testing.

Dr. Caudle:
And now I understand that there are some differing perspectives on triaging between primary HPV screening and co-testing. What's your take on this, and how did you come to this position in your own practice?

Dr. Harper:
I think it's important to note for cervical cancer screening that we have moved away from algorithmic steps in how to screen women and what to do with them after they have a normal or an abnormal screen. And much of the evidence that has gone into co-testing has been

based on that algorithmic stepwise process. We now have plenty of evidence that allows us to have women followed for at least five years – some 10 years – in using both HPV testing and in the combination of HPV and cytology co-testing. And through this database, we are able to establish risk thresholds for when a woman is at particular risk for developing what we call CIN 3 disease. That stands for cervical intraepithelial neoplasia grade 3. That is considered the real precursor to cervical cancer. That is the goal of cervical cancer screening: to primarily detect the CIN 3 and to treat it so that cervical cancer is prevented. So with this new database, we now have developed risk thresholds that say that should your risk of CIN 3 or worse be at or greater than 4 percent, then you would need to go straight on to new testing. That puts you at risk for CIN 3+. That means you would need to go on to colposcopy. You'd need further workup. So that 4 percent level becomes very important. Now the question is: how do you get to that 4 percent level, and which kind of testing gets you there? We know with primary HPV testing that if you test positive for 16 or 18, you are automatically above that 4 percent threshold and will automatically go to colposcopy for further workup. We know that if you are negative for all of the high-risk HPV types that you are much below that 4 percent threshold and that you can be followed up with continued primary HPV testing at 5-year intervals.

The question becomes: what happens to those women who are positive for the 12 other high-risk HPV types that are not 16 and 18, and how do we manage those women? And so that is when different triage strategies take place, and that is the value of those triage strategies.

Dr. Caudle:
And just to level-set, can you run us through the various methods available for triage, such as host and viral methylation, dual staining, extended genotyping, and so on?

Dr. Harper:
When we look at methylation, we know that methylation is intimately involved in oncogenesis. We know that methylation happens both amongst the HPV DNA and in the human host's DNA. With increasing HPV vaccination rates, we will have less and less HPV 16, 31, and 33 types, and with that, we will eliminate much of the need for having HPV-type methylation as a predictor of whether or not oncogenesis is happening. But that's only if we get HPV vaccination rates up at a much higher rate than they are now. Until then, we'll need both the host and HPV methylation in order to be able to tell us whether or not oncogenesis is happening. Post-methylation will always be constant and will be the methylation triage mechanism that we will be able to count on once we have full vaccination of our populations.

Dual staining looks at Ki-67 and p16 as proteins that can be stained for within the cells, and that has shown great discrimination between those women who are at increased risk for oncogenesis and those who are not. We know that dual staining is a triage test that's FDA-approved that will push women who are 12 oncogenic high-risk type positive (non 16-18 high-risk HPV subtypes) above the 4 percent threshold. We also know that dual stain, when it is negative, is actually a better safety tool than is cytology that is read out as normal. We know that these women who are dual-stain negative have a much lower risk of CIN 3+ than even do the women who have normal cytology.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Advances in Women's Health* on ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Diane Harper about the new frontiers in cervical cancer screening.

So Dr. Harper, let's dive a little deeper into dual staining as one of the methods we discussed. What are the proposed advantages of this method as supported by recent literature, such as the IMPACT trial?

Dr. Harper:
When we look at studies such as the IMPACT trial, which followed women for a year, we see that those women who were dual-stain negative are at even lower risks for CIN 3 development than women who have a normal cytology. And so it is quite predictive and quite reassuring to women whose dual stain is negative. On the other hand, for those whose dual stain is positive and read as positive, we know that that provides that secondary level of triage for those women who weren't quite at the 4 percent threshold to all of a sudden push them above that threshold. So if they're dual-stain positive, it's a very good indicator that they need to go on to colposcopy. So it does provide us with great information, and it depends on where you want to use it in the triage strategy, whether you want to use it

after a positive, pooled HPV test, which just says, yes, they're positive for HPV, but we don't know what type. We can use dual stain with that, and it gives us good stratification. We can also use it after the HPV genotyping for those 12 other high-risk HPV types, and that gives us good stratification. We can also use it with HPV and cytology, but that's a lot like putting on belts and suspenders. So we don't really need the cytology part to have the benefit of having dual staining.

Dr. Caudle:
And if we focus back on extended genotyping, what do you see as the most prominent benefits and limitations to its inclusion in cervical cancer screening?

Dr. Harper:
Extended genotyping is important because we can actually see which women are 16 and 18 positive. Those are the women who are at greatest risk for CIN 3, or worse, and those women can immediately be sent to colposcopy for follow-up. If a woman is HPV negative, if she has none of the 14 high-risk HPV types, we know that she's safe and that she can have routine screening in five years. If she's positive for the 12 other high-risk HPV types, we know that she's in an intermediate risk, and we are able to help counsel her on coming back for follow-up and/or the appropriate triage to be done immediately at that time. So understanding the genotype provides us with risk stratification, which becomes very important for patient management.

Dr. Caudle:
So, Dr. Harper, before we close, I just want to come back to where our discussion started on primary HPV testing. On a practical level, what do you think will be needed next to help clinicians implement this approach going forward?

Dr. Harper:
That is a great question, Dr. Caudle. I'm going to address it on three different levels. The first level is level of the patient, the second level is the level of the physician, and the third level is the level of the health system. On the patient level, we really have to do a good job at communicating with our community advisory boards and our community advocacy groups about what primary HPV testing is and that the results they will be getting back from their physician from their cervical cancer screens will give them a risk indication based on HPV typing. It is really important that women understand this and that women are our partners in screening, and not just the objects of our screening. The second level is the physician level, and that means that all women health providers really must unite in giving the same message: that the evidence shows us that primary HPV testing is a much more sensitive test, and it has fewer harms associated with extra referrals to colposcopy for our average-risk women. As physicians and as providers that provide cervical cancer screening for women, we must be on the same page. And then finally, for our healthcare systems, there are many things that need to be done in order for this to happen smoothly: the IT work that has to happen on the laboratory side, the order forms, the way in which we have what we call BPA – best practice advisories – that get sent to physicians so that as they are practicing in their busy clinical lives, that this can be facilitated for them without extra thought and without extra time spent in trying to figure out how to make the order happen. So with the bringing together of all three of these groups – our women, our patients, all of our physicians and providers for women's healthcare, and our healthcare systems – I think that we can effectively bring primary HPV screening to all women who are of average risk.

Dr. Caudle:
Excellent. Well, given the high prevalence of cervical cancer, it's great to know that these and other advancements can help us prevent and detect it much sooner. I'd like to thank my guest, Dr. Diane Harper, for joining me to discuss the latest updates in this field. Dr. Harper, it was great having you on the program today.

Dr. Harper:
Thank you.

Announcer Close:
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