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Clinical Utility of HPV Genotyping and Primary Screening

Announcer Introduction:

You're listening to REACHMD. Welcome to this Medical Industry Feature entitled, "Clinical Utility of HPV Genotyping and Primary Screening" sponsored by Roche Diagnostics. This program is intended for physicians.

Dr. Birnholz:

As evidence continues to accumulate about the risk of cervical cancer from persistent infection with high-risk types of human papilloma virus, particularly 16 and 18, professional associations have kept pace with updated guidance based on new data and testing methodologies. Today, high-risk HPV genotyping is included in standard screening algorithms, and genotyping of HPV 16 and 18 is making a positive impact on patient management in multiple ways. This is ReachMD. I'm Dr. Matt Birnholz. Joining me to discuss HPV genotyping and primary screening is my guest, Dr. Lee Shulman. Dr. Shulman is a Professor of OB/GYN at Northwestern Medical Center in Chicago, Illinois. Dr. Shulman, great to have you with us today.

Dr. Shulman:

Great to be here with you today, Matt. Thanks.

Dr. Birnholz:

Why don't we begin our discussion with a look at your current methodologies for cervical cancer screening? What is the cervical cancer screening protocol at your institution specifically, and does your screening methodology vary for different aging groups?

Dr. Shulman:

We were an early adapter of HPV in our cervical surveillance algorithm primarily because myself and my colleagues recognized that while the Pap smear was developed for, and was incredibly successful in detecting early cervical cancer, it was not that good in risk assessment; meaning for those women who don't have cancer but may be predisposed to developing it later on in their lives, looking just at the cells just was not an exemplary way of being able to identify those women who would go on to develop cancer. That being said, there are several HPV algorithms out there. Myself, I tend to use what's called primary screening. Many of my colleagues use HPV co-testing.

Dr. Birnholz:

I'd like to be able to talk a little bit more about the primary screening and co-testing using the practices specifically, but let's turn to the HPV genotyping. How have you incorporated this into your screening protocol?

Dr. Shulman:

Well originally, HPV was just used as a determinant of general high risk versus low risk. It's become also very clear with large numbers of very good studies, that not all HPV genotypes are the same; meaning not all of those high-risk types will go on and lead to cancer either in the same frequency or in the same time period. And long story short, those women who are infected with HPV types 16 and 18 are clearly far more likely to go on to develop severe dysplasia or even malignancy in a more rapid fashion than those women who may be infected with one of the other high-risk HPV types. So, for me, it is important to know not only does that woman have an HPV infection with a high-risk HPV type, but for me it's also important to know what type of HPV she is infected with, because again, with a more virulent form of HPV, specifically types 16 and 18, I want to evaluate that woman and monitor her more closely than a woman

who's infected with a less virulent high-risk type.

Dr. Birnholz:

And when considering the algorithms for co-testing and primary screening, how does primary screening differ?

Dr. Shulman:

Instead of adding HPV testing to a cytological process, it is essentially using, just the way it sounds, primary screening. We save cytology for one particular situation, which I'll go over in a moment, but instead of primarily looking at cytology at the cells, we're primary assessing the HPV. So, if she's got negative, if there's no high-risk HPV, then it's recommended that the next assessment be done in approximately 3 years. If she has a positive result for either 16 or 18, it's recommended that regardless of what the cells look like, to go ahead and perform colposcopy and evaluate and get a diagnostic assessment at that point. The interesting thing for me is, where does cytology come in, and that's for the patient's who's got a non-16, non-18, high-risk HPV. So, there are, in a sense, 14 high-risk HPV types. These are the 14 that are oncogenic; that can go on and lead to the development of a cancer, 16 and 18 more virulent, more quick. The other 12, not as virulent and not as quick. And so, if she comes back with a high-risk HPV that's not 16 or not 18, it's then recommended, again it's a liquid-based assessment, tissue collection, it's then recommended to then go ahead and look at the cells. If the cells are normal with, again, a non-16/18 high-risk HPV, it's okay to wait a year and reevaluate her again. But if the cells show anything from ASCUS going forward, so ASCUS, LGSIL, HGSIL, it is then recommended to go ahead and perform colposcopy.

Dr. Birnholz:

You touched briefly upon the virulence of HPV types, specifically 16 and 18, and I want to focus on that for a minute because the significance of HPV types 16 and 18 has become more universally recognized in the healthcare community. We know that much, but it's not entirely understood how and why patients get managed differently who are positive for HPV 16 and 18 than those who are positive for other high-risk types, such as HPV 45. Can you touch upon that and why 16 and 18 matter so much in the treatment paradigm?

Dr. Shulman:

Well, they matter so much for two reasons. First of all, the data that we base these differences on is not theoretical data. It's actual clinical data; and we've collected clinical data on specific HPV types really since the early 1990s. So, we have a large library of excellent data and more important than just excellent data, from large prospective studies like ATHENA that we've been able to assess the patients with negative Paps, patients with negative HPVs, performing colposcopies on ostensibly normal patients, to see what are the downsides. And I think the literature is rather clear that says that paying attention to the actual type of HPV affords us as clinicians, and affords our patients, a far more accurate assessment both of what is the implication of a positive result, and perhaps even equally as important something we don't think about, I'm going to use the word, the power of the negative result. The power, the ability to say that, "Your HPV is negative," with the implication for that is that even if you were to get infected after this assessment, if we, and you're not supposed to, but in the algorithm, the next collection can be 3 years from now. Because of that negative result, the likelihood of there being adverse outcomes in 3 years is incredibly remote. So, we have a better predictor of disease and we have a better negative predictor of normalcy when we, in fact, look at genotyping algorithms.

Dr. Birnholz:

Well, if you're just tuning in, you're listening to ReachMD and I'm your host, Dr. Matt Birnholz. I have the pleasure of speaking with Dr. Lee Shulman on the topic of HPV genotyping and primary screening. Earlier we spoke a bit about the cervical cancer screening protocols at your institution and how you've incorporated genotyping for HPV type 16 and 18 into your methodology; a really great run through of the screening algorithms and protocols that you've instituted both on co-testing and primary screening. Why don't we focus on HPV primary screening again and talk a little bit, maybe in more detail, about how primary screening compares to conventional cytology screening? It seems like there are some advantages there.

Dr. Shulman:

Well, in reality, what I always felt was the greatest advantage was the simplicity. Instead of a complex decision-making tree, you have 1 of 3 results. You have a negative HPV in which case no further assessment is needed for 3 years, or no further cervical collection is needed for 3 years. You have either a positive 16 or a positive 18, in which that woman is referred or has performed a colposcopy. Or, you have a positive non-16, non-18 HPV, in which case the laboratory will reflex to cytology and if the cytology is anything other than normal, then again, colposcopy is the appropriate next step for the evaluation of that patient. And perhaps the other difference between primary screening and co-testing is that we initiate the use of this algorithm at the age of 25, rather than the age of 30. And the reason for that is that there is a not inconsequential number of women between the ages of 25 to 30 that have severe dysplasia as a result of an HPV infection, and by lowering the assessment to 25 from 30, we are able to maintain the sensitivity and, well slightly improve the

sensitivity, and maintain the specificity of the algorithm compared to co-testing. So, a somewhat more accurate screening for cervical risk, for primary screening, and for me, the greater simplicity. What really cannot be overstated is the importance of a more powerful negative predictor so as to reduce the performance of unnecessary interventions in women.

Dr. Birnholz:

So, Dr. Shulman from your point of view, how has primary screening changed other people's perspectives on cervical assessment and surveillance in practice?

Dr. Shulman:

When we take a look at cervical assessment, a lot of clinicians say, "You know, I'm not happy with having to do a Pap every 3 years, and not every year," and again, there are some clinicians who don't understand why a test done perhaps every 3 or even 5 years is better than a test done every year. I think it's important to maybe understand that cervical surveillance is a yearly process. How often you collect the specimen has to do with the algorithm you're using. But every year that woman comes in for her annual visit, whether it be for contraception, or menopause, or whatever is the reason for her visiting, for her annual visit, for pelvic assessment, etc., you're doing cervical surveillance. For example, a patient I see (sic) yesterday had a negative-negative Pap. I had not seen her the year before. She had negative cytology, negative HPV, so I tell her that and tell her that her next cervical sampling, if it was in 2015, in 2018 to 2020, and that it's okay that we're not collecting a sample today. And I must tell you, from my patients here in Chicago, I have not had any problems with women saying, "No, that's unacceptable, I want a Pap smear done." A lot of women come in saying they want that Pap smear, but the phrase "Pap smear" has as much become a euphemism for pelvic exam or gynecologic exam than anything else. And once I explain how the process goes, I've had almost universal acceptance of how we're monitoring them and the kind of care that we're providing to her.

Dr. Birnholz:

Well, before we wrap up our discussion today, you've given us a great background on both the history and the present state of testing in screening for HPV. But what about looking towards the future? What do you think the future holds for cervical cancer screening?

Dr. Shulman:

The one aspect of cervical cancer screening that has somewhat simplified things is the fact that 98/99+% of cervical cancers are associated with HPV infections and, obviously, associated with high-risk HPV infections. That is not true with other HPV-specific cancers: anorectal, oropharyngeal, etc. The frequencies, the percentages of detectable HPV infections in those cancers is less. So, we've been actually somewhat fortunate that HPV is that consistent finding with cervical cancer and that has allowed for us to develop these incredibly effective screening protocols. I think, clearly, the future is going to be finding more precise molecular findings, molecular biomarkers, etc., that may lead to even better detection of those HPV infections that are more likely to lead to severe dysplasia and malignancies. That's an answer, Matt, that I could actually give for a variety of disease conditions, prenatal diagnosis, non-cervical cancer assessment, the erstwhile liquid biopsy. There are a variety of cancers and of conditions that we are becoming far better at detecting because of a far better understanding of the molecular components of, in this case, infection and cellular change as a result of infection.

Dr. Birnholz:

Well, with those forward-looking thoughts, I very much want to thank my guest, Dr. Lee Shulman, for joining me to discuss HPV genotyping and primary screening. Dr. Shulman, it was excellent having you on the program.

Dr. Shulman:

I appreciate it, Matt. Thanks very much.

Announcer Close:

You've been listening to REACHMD. The preceding program was sponsored by Roche Diagnostics. If you have missed any part of this discussion, visit ReachMD.com/HPV. Thank you.