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This medical industry feature, titled “The Importance of Extended Genotyping in Cervical Cancer Screening: The Special Case of HPV 31” is sponsored by BD. This program is intended for physicians.

Your host is Dr. Matt Birnholz.

Dr. Birnholz:
This is ReachMD, and I’m Dr. Matt Birnholz. Joining me to discuss the role of HPV extended genotyping in screening for cervical cancer is Dr. Mark Stoler, Professor Emeritus of Pathology and Clinical Gynecology at the University of Virginia Health System in Charlottesville, Virginia. Dr. Stoler, welcome to the program.

Dr. Stoler:
Thank you, Dr. Birnholz. Pleasure to be here to discuss this topic.

Dr. Birnholz:
Yeah, great to have you with us. So, to start us off, Dr. Stoler, can you just give us a high-level overview of HPV extended genotyping?

Dr. Stoler:
Well, the use of HPV testing and cervical cancer screening and management, and now the use of genotyping, in particular extended genotyping, is a great example of the field following the science and the data to improve patient management. Originally, HPV assays, which were brought online to increase the sensitivity of screening since we’ve recognized the limitation of Pap cytology alone grouped the thirteen or fourteen HPV types that were responsible for about 95 percent of cervical cancer and precancers as one big group. So, HPV-negative women were reassured that they didn’t have cancer better than a Pap smear alone, and HPV-positive women could be focused on in terms of how do we manage the positive patients, just like how do we manage positive Pap smears. Fast forward ten years of good epidemiology and we know that HPV 16 and 18 are responsible for 70% of cervical cancers alone. This is why the HPV vaccines are focused so much on HPV 16 and 18 prophylaxes. And another ten years of really good, worldwide epidemiology is demonstrated that the twelve other types that are left over after HPV 16 and 18 is not called out in the current clinical assays that do partial genotyping, really have differential risks. And so, the concept of extended genotyping is an HPV clinical assay that calls out types other than 16 and 18 and it focuses then on the individual genotypes that are present within the patient, beyond 16 and 18, to look at those specific risks associated with those specific genotypes.

Dr. Birnholz:
Well, that’s an excellent foundation that you’ve just given us to help better understand this emerging role for extended genotyping, but I’m interested in whether HPV extended genotyping

currently aligns with the cervical cancer screening guidelines out there, as well as patient management guidelines, for that matter. What can you tell us?

Dr. Stoler:
Well, the foundation of the guidelines, both screening and management, is the concept of equal management for equal risk. So historically, we weren't managing patients with different elements of their age, their genotype, their Pap smear status, in terms of whether they could go into follow-up or needed to go to colposcopy or have a biopsy or even have treatment. So, we really, over the last decade, tried to focus and establish the thresholds of risk for how we manage patients. And so, in the current guidelines, partial genotyping is everywhere. 16 and 18 are very important. Well, it may surprise your listeners that a woman whose HPV 16 positive, who has a normal Pap smear, has a 10 percent to 20 percent risk of having CIN 3 – a very high risk that requires finding that CIN 3 and preventing cancer development. But now we're extending the conversation, where we're really trying to adapt the guidelines to the latest good data, which shows that different genotypes beyond 16 and 18 have similar risk to 16 and 18, that have been masked in the prior group-typing assay.

Dr. Birnholz:
Well, that's interesting. I want to dig into that a little bit further, because I understand that only HPV assays with extended genotyping can identify high-risk genotypes beyond HPV 16 and 18. So let's say that a patient does test positive for another genotype, such as HPV 31. How would that impact patient management?

Dr. Stoler:
Well, HPV 31 is a great example because in the US, HPV 31 is the type that's most commonly seen in high-grade precancer and cancer, after HPV 16 and 18. In fact, it's higher prevalence of higher risk in precancer than HPV 18. So, it would make sense that if we're doing something for 16 or 18, different than the other types, that perhaps we should manage HPV 31 similarly. It's also interesting that HPV 31 is the closest molecular relative to HPV 16, so you're seeing the interaction of the basic biology and pathogenesis played out, in terms of cancer risk in the population.

Dr. Birnholz:
And I imagine, Dr. Stoler, that when we speak of prevalence, we're also not in the same playing field that we may have been, let's say ten years ago, in the context of declining rates of HPV 16 and 18, as vaccination rates increase compared to other high-risk genotypes like HPV 31. Can you speak to that a little further?

Dr. Stoler:
Yeah, that's such really an important point, Matt, because vaccination is really changing the prevalence of the genotypes in the population, and it's that interaction between the genotype you're infected with and your risk of cancer development that drives the screening and management guideline recommendations. So, we know that the quadrivalent HPV vaccine, which focused on HPV 16 and 18 because it's responsible for 70% of cervical cancer, has really driven down the prevalence of HPV 16 and 18 in the population. The HPV 16 alone is down

over 60%, and that's without very high coverage. We're only at about 50-60% coverage in the target teenage populations in the country. So as the prevalence of the most oncogenic types drops, the whole equation in terms of balancing risk versus type shifts towards the types that are residual in the population, that may not be covered by the quadrivalent vaccine. So, for instance, HPV 31 would assume increasing importance as a relative proportion, given that 16 and 18 prevalence is dropping.

Dr. Birnholz:
And in the context of a positive test for HPV 31, are the next steps and treatment paradigms roughly the same, or identical to how we approach 16 and 18 positive tests?

Dr. Stoler:
Well, I think that's what this conversation is about. The data say they should be, so the management guidelines need to evolve and become updated, or we have to, you know, get at the concept of splitting out the risk in the twelve other in some other manner. But extended genotyping is already available in assays that have that capability to get directly at those epidemiologically now well-established risks.

Dr. Birnholz:
Excellent. Great point, Dr. Stoler.
For those just joining us, this is ReachMD, and I'm Dr. Matt Birnholz. Today I'm speaking with Dr. Mark Stoler about extended genotyping in the context of cervical cancer screening, and the importance of identifying other high-risk genotypes, such as HPV 31.
So, Dr. Stoler, I want to come back to the question of impact for this type of testing and compare the clinical utilities of extended genotyping versus assays with partial genotyping that pool results. Can you give us some more detail on that?

Dr. Stoler:
Well, extending our concepts in this conversation, about equal management for equal risk, the spectrum of risk associated with the fourteen types in the clinical HPV assays is quite large – more than ten to twentyfold variation among types. So, HPV 31, which has risks of developing precancer and cancer in the short term, if not prevalent precancer and cancer can have ten times the risk of another one of the types in the in the pool of twelve others such as HPV 59, which has a risk that approaches zero in the immediate or short term, meaning in the year following this positive screening test. So, it makes sense, then, to use extended genotyping information if it's available to stratify those risks and to treat patients with high risk differently than patients with low risk. Meaning the high risk patients go to immediate colposcopy while you have them identified, to maximize disease ascertainment and treat that precancer and perhaps find that rear, already prevalent cancer that might be present in the screening population, whereas those risks are so low, that referring, you know, all the HPV 59 positives, or all the HPV 45 positives even alters the balance towards, you know, excessive referral to colposcopy and low yields at colposcopy, such that it's probably better to follow those patients for a short period of time, like a year to see if they have persistent type-specific infection.

Dr. Birnholz:

And I'm gathering, based on what you're saying, that there's a risk, if you will, of risk masking that is going on with pooled analysis versus the ability to call out or identify specific other high-risk genotypes. Is that true?

Dr. Stoler:
Yeah, I think it is true, although, you know, relative to the risks of HPV 16, you know, historically these were acceptable risks, but now we understand better that, you know, some of the types are equally risky, particularly HPV 18, or even a little more risky than HPV 18. They have different prevalence's than HPV 18, but that equation that establishes risk in the population that drives the thresholds for management really would speak to if you know someone's HPV 31 positive, manage them like 16 and 18, not like HPV 59.

Dr. Birnholz:
And I think you're alluding to this really well, but I just want to hone in on HPV 31 a little further and get a better sense as to why this particular genotype is so critical to report individually.

Dr. Stoler:
HPV 31 is the next most common type in high-grade precancer and cancer of the population. It's molecularly most similar to HPV 16, which is probably driving that. And so, because it's so common, and because its risk profile is similar to or just between 18 and 16 it makes sense that we take those patients to colposcopy rather than what we're doing now, which is referring them for one year follow-up.

Dr. Birnholz:
Well, Dr. Stoler, you've given us a lot of great insights, in a short time, regarding this new role in the emergence of extended HPV genotyping and giving us a better sense of HPV 31. But before we close, I want to open the floor to you for any additional takeaways that you want to share with our audience.

Dr. Stoler:
Well, I think the first high-level takeaway is the importance of HPV testing in patient management. In my opinion, nobody should have cervical cancer screening without having an HPV test, and around the world people are using HPV testing as the first test now, rather than the Pap smear. Once you're HPV tested, an HPV negative woman is highly reassured, much better than a Pap, in terms of not having an immediate risk for cancer or precancer. HPV positives, on the other hand, we know that there's stratified risk within the fourteen types we're testing for, and we now know, based on really good data, that types other than 16 and 18, which have been called out in the assays and management protocols – screening and management protocols for more than a decade – now have similar risk profiles, something we didn't know before. And so, as the guidelines evolve, the concept of equal management for equal risk really dictates that if we can know somebody has HPV 31, we should manage them according to their relative risk, which is similar to 16 and 18.

Dr. Birnholz:

Well, clearly, everything we've covered here today only underscores further just how important it is for us to stay up to date on cervical cancer screening which seems to be changing at fantastic rates. And with that, I want to thank my guest, Dr. Mark Stoler, for helping us better understand the importance of extended genotyping and gaining new insights on HPV 31 along the way. Dr. Stoler, it was fantastic having you on the program today. Thanks so much.

Dr. Stoler:
Well, it was my pleasure to be here, and I hope people find this discussion useful.

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