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The Future of Cervical Cancer Screening: HPV Extended Genotyping, Risk Stratification, and Beyond

ANNOUNCER INTRODUCTION

Welcome to the Omnia Education CME activity, entitled The Future of Cervical Cancer Screening: HPV Extended Genotyping, Risk Stratification, and Beyond presented by Dr. Warner Huh, recorded live at the Women's Health Annual Visit in Dearborn, Michigan.

This activity is supported by an independent medical educational grant from BD Life Sciences.

Dr. Huh

I am going to talk about the future of cervical cancer screening and what that looks like. As far as my disclosures, I receive consulting fees from Incell Dx and TheVax, both of which are completely irrelevant to this lecture, but I just wanted to disclose that to this group.

The objectives are really multiple, one of which is to kind of teach this group about evolving diagnostic tools that are used for cervical cancer screening and what exactly extended genotyping looks like. I will talk about that in a second further. I will talk about some of the barriers that we face in terms of using some of these technologies. Dr. Wright talked about this earlier, but when he originally published Co-testing back in 2004 in the Green Journal, it has taken us well over a decade to achieve greater than 50% utilization of co-testing, so some of these things happen at a truly glacial pace. I am going to talk about the harmonized guidelines. For those that know this, back in 2012 both the American Cancer Society, the ASCP and ASCCP as well as United States Preventive Services Task Force actually finally have guidelines that are largely harmonized, so you did not have one guideline that said one thing and another guideline that said another. Lastly, I am going to talk about how some of these extended genotyping methods can be used to stratify risks but also decrease the use of treatment as well as colposcopy.

In order to understand screening – and this is something that is really particularly tough to explain to patients – as an oncologist, in essence, sees the downstream spectrum of patients from screening, which is those women who get cancer whether or not they have not been screened or if they fall through the cracks of screening is that one, you cannot prevent all cancer with screening, whether it is cervical cancer, breast cancer, or colorectal cancer. That is absolutely impossible, but unfortunately, in this country, particularly with the lay public, there is a belief that if we over screen or screen appropriately then we will prevent all cancer and that could not be further from the truth.

Over the last essentially 50 years, cytology is the benchmark for screening performance and still is. Much of our knowledge, in terms of how screening works particularly in the setting of cervical cancer prevention, is based on cytology and cytology alone. Now, that is changing, because over the last five years there have been multiple papers that have been published on the value of co-testing as well as primary HPV screening, but we realize that the benchmark is still cytology. Realize that women who are at similar risk for CIN3 should be managed similarly. It is this concept of similar risk/similar management. So, if you have woman A and woman B who have the same risk, those two women really should be treated in the exact same way. You are going to see that theme over and over again in the upcoming years as we change our iterations of our treatment guidelines.

What is the purpose of genotyping? What do I mean by genotyping, first, because there may be some people in the room that have no idea what I am talking about. Many of you have been utilizing HPV testing or specifically high-risk HPV testing. Depending on the panel

and depending on what data source you use, there are generally 13 or 14 high-risk types that are associated with a higher risk of developing cervical cancer. When we say high risk that does not mean behavior. That means the association in terms of epidemiology between having that type and getting cervical cancer. Genotype is really looking at those specific types. You have heard about type 16 and type 18, but what about the other 13 types that are out there that are relevant?

The way we use genotyping now and that we will likely use in the future are threefold. One, is really to identify those women who need immediate colposcopy. You get a certain test result that comes up with a certain HPV result combination, well that woman may need to go straight to colposcopy and get a biopsy. The second thing is really to identify those women who have invasive cancer now. That is quite obvious, and the third thing is really to identify those women that could be followed over a 6-12 month period, and so to kind of like basically to steal my thunder from the very beginning, in the future, in essence, these three things on this slide will constitute the three management strategies for really all of our abnormal screening tests in the future. Immediate colposcopy, immediate treatment, or whether or not the patient could be safely followed. It is going to be that simple, but the choices to get to that may be complex.

When you detect CIN3, it is ultimately a trade-off – and again this was discussed earlier – it is a combination of looking at sensitivity and specificity. I think to understand this topic, you have to understand what sensitivity and specificity is. Most people in the room do, but for people in the room who do not, I would look at it this way. Sensitivity is really a reflection of your false negative rate and specificity is a reflection of your false positive rate. So, low sensitivity means you have a high false negative and vice versa.

When you look at screening – this is not just true for cancer screening and cervical cancer screening, this is true for all screening, irrespective of the disease setting – you want a highly sensitive test. You want to test with a low false negative rate. Why – because you do not want a missed disease. That is partly the problem with cytology, as Dr. Wright talked about, is the sensitivity is actually much lower than we originally thought, and so when you have a woman that you say that, “Oh, your Pap is fine; you have a nil Pap; you are okay.” Well, in reality over 50% of those women may not have really normal findings and may actually harbor disease and you simply do not know it. When you triage patients – so, in other words, when you get a test that basically is looking at an abnormal screening test, well in that setting you want that test to have a balance between sensitivity and specificity as well. That is why these things are really, really important and we spend so much time on them, but at the end of the day, you do not want to miss disease, particularly with a screening test.

What about surrogate measures? In 2017, the surrogate measure, whether you like it or not – I am going to talk about this shortly – is really the number of colposcopies. It is about the number of colposcopies that are incurred or you prevent with a specific screening measure. For me, this is just my personal opinion I am not sure that colpo was really the right endpoint when we made the screening guidelines, and this was actually discussed at length in the screening guideline meeting when all the experts got together. Most of us do not really consider it to be a true harm. I am not discounting the fact that, one, it is uncomfortable; it is anxiety provoking; it can identify disease that can regress and obviously is expensive, but really if you look at it, is colpo really the right harm measure and that this is something that is constantly being debated today.

When you look at basically balancing CIN3 and colposcopies – see the patient on the left? Obvious to most people who do colpo, probably needs a biopsy or two. Right? The patient on the right, if you were just to look at their cervix, you may be like, “Yeah, it does not look so bad. Maybe I am just going to do an ECC.” Right? But again, we have to balance all these pieces together – the screening piece, the triage piece, the colpo piece and obviously the histology that is obtained from these colposcopic biopsies. It is really a balance, and the question is, how does genotyping play an ultimate role in that?

Over the last several years, what we have learned is that basically different combinations of tests carry different types of risks for that individual woman – risk currently and risk in the future. As you can see in the far left, you have a woman that is Pap negative and HPV negative – what we call co-test negative – and that woman has a tiny risk, basically a 0.1% risk of having CIN3 or worse, and what is the current recommendation? Rescreen every five years. We will talk about the rescreening interval probably either later on in the Q & A session for this or in the later session this morning. Then, you go all the way to the right of the curve basically where women with HSIL have up to a 50% risk of having CIN3. In reality, that might be on the low side. What do we currently recommend? We recommend that those women undergo an excisional procedure, specifically a LEEP. Then, there is everything in between.

What we are going to talk about is not so much the numbers but how these different testing combinations match up with one another. If one testing combination comes up with a risk of, let’s say 18-20% and another testing combination comes up with this exact same number, 18-20%, then what we are going to tell you is that you should probably manage that patient the exact same way, which on this slide is just to go straight to colposcopy. So, yes, it has gotten extraordinarily more complicated. You know, Tom Wright is in the room and he actually wrote the first iteration of our treatment guidelines and if you look at his guidelines and what the most recent guidelines are, they are exponentially more complicated. Why? Because we have acquired that much more data to inform us in terms of how to make those decisions. It is the issue of precision that we are dealing with and how do we pass that precision on to providers like yourself

to make good decisions?

Co-testing with genotyping: Originally when co-testing was recommended, what was recommended is that women who are Pap negative and HPV positive for those 13 or 14 high-risk types, we get repeat testing one year later. Then several years after that, there was an understanding that if you were 16, 18, and now perhaps 45 positive, then basically you should go straight to colposcopy and not wait one year. Why? What we know is that those women who have 16, 18 and 45 are at a much higher risk for having disease, not only today but also in the future, and so currently this is one of those recommendations. You may work in a lab that utilizes genotyping specifically for type 16, 18 and 45 and again the recommendation is if you get that testing, you go straight to colposcopy, and if you happen to have a normal Pap and you are positive for the other HPV types but negative for 16, 18 and 45, then you have co-testing done in 12 months. You can already see how much more complicated this has become in a short period of time.

When you actually look at the actual risk of CIN3 in women who have normal cytology, it is not surprising that if you have a negative HPV result in conjunction with a woman who has a normal Pap, the risk is less than 1%. This is based on the Athena trial, which is a large FDA registration study that was sponsored by Roche as well as the CLEAR Study, which is a different assay called the APTIMA® assay, which is also a FDA registration study that was sponsored by Hologic and so what you see is that when you become HPV positive, the risk goes up to about 4-5%, but where you see a huge jump is those women who are 16, 18 and 45 positive. The risk is at least 10%, compared to the other high-risk types, which is only about 2-3%. What you are going to see over and over again is how important it is, particularly for you to genotype for 16 and 18 and in the second half of the talk, the talk about the relevance of genotyping for the other types that are not 16, 18 and in this case 45.

Are genotypes other than 16, 18 and 45 important? The answer is yes. You cannot talk about screening without vaccination in the same breath, particularly now. Even though in this country vaccination rates are still appallingly low compared to other industrialized nations worldwide, particularly the UK, Canada, New Zealand, etc., the rates still continue to climb, and we have no reason to suspect that that rate is going to go down.

Originally when Gardasil 4 or Cevarix came out, we were looking primarily at 16 and 18, which prevented about 70-75% of all cervical cancers in the United States and worldwide. Well, presently in 2017, there is really one vaccine that is available and that is Gardasil 9 that is produced by Merck. Yeah, you can still get Gardasil 4, but Merck is not producing it anymore, so really what we are stuck with is Gardasil 9, which arguably for women is a better vaccine, because now you are going from basically 70% protection to as high as 92-93% protection by adding these five other types that are relevant to the risk of cervical cancer.

What we know is that these genotypes are important. They are important in terms of adding risk, but what about screening? Is understanding whether or not a woman is positive for 52, 33, 31, 45, etcetera, does that affect management? Now, if you had asked me that question five years ago, I would tell you categorically no. There is no way in this country that a provider can manage all of that information in a reasonable timeframe in a way that was going to be helpful and appropriate for women. What we have done is we have required a lot of data over the last five years that have highlighted this issue of extended genotyping and that is really the goal of this talk to show you how much has changed in a short period of time.

What exactly is the association with HPV and cervical cancer? Well, here is the thing. This is a study that was published by Nubia Munoz back in 2003 in the New England Journal of Medicine. It is probably one of the most often cited papers in HPV cervical cancer epidemiology in history. Basically, this comes from IARC, the International Agency for Research in Cancer and it included over 2,000 women with cervical cancer, genotyped their cancers, interestingly, there were not that many cancers from the United States so this is maybe not a great representation in the United States, but basically looked at the risk of cervical cancer and the specific genotypes that were investigated. You can see at the very top of the list is HPV 16 followed by 33 and 88. There is an odds ratio of 435. For those that do not understand odds ratios, when you read these studies in CNN that coffee causes cancer and you see it says it has relative risk or an odds ratio of 1.5, we are talking about a 50% increase when we talk about this.

When you talk about the relationship between 16 and cervical cancer, we are talking about basically a 44,000% increased risk of getting cancer. What is important to recognize here is by far 16 is the strongest, but also recognize that 16 is the most prevalent and you will see why that is important as well. We are talking about astounding epidemiologic and statistical relationships between HPV and cancer, but here is where we screwed up. Where we screwed up in the mid-2000s was that when Merck produced Gardasil and started marketing it, we started telling women that HPV caused cervical cancer, but what we know is that it really does not. What causes cervical cancer in reality is a persistent infection. The vast majority of women in the United States who get HPV, which are millions and millions of women, a tiny single-digit percentage of those women will actually go on to develop clinically significant disease. So, in a way, we have miscounseled women in the public as well as providers, but realize that singular HPV 16 infection that goes away on its own, that woman is not going to get cancer, but a woman who is persistently positive for 16 over time probably has a much higher chance, and there is data to actually support that. Again, this is a study by Cossette Wheeler, who is from New Mexico. The state of New

Mexico actually has the only state-based registry in terms of looking at Pap results, HPV results and outcomes in terms of screening. The unfortunate thing in this country, unlike the UK, Australia, Sweden and the other Scandinavian countries is that we have no idea of how we are doing in terms of screening and tracking disease. We have no central registry, and that is largely because of how our insurance works in this country, but what you will see here is, again, when you look at these odds and ratios, you see significantly high odds ratios for types 33, 16, 18 and 31. So again, it points out to why these types are ultimately important in terms of stratifying them, but again, we see over and over again that women who have high-risk HPV are at higher risk for having disease.

This is another study that was published by Jack Cuzick. Jack Cuzick is an epidemiologist in London. He has a great interest in cervical cancer prevention and HPV. This is a study that used an assay that is not really available here in the United States as well as using a PCR-based assay. He looked at about 1,000 women undergoing colposcopy with abnormal cytology, and again what you will see here in terms of looking at specific genotypes, types of HPV and the positive predictive value in terms of type is what you will see here is that type 16 and 18 rise to the top as well as 31 and 33, but at the very top, yet again, is type 16 as well as 33 and so over and over again what you are seeing is how important 16 is to this discussion.

Another study that was done in the United States is a study that was published by Mark Schiffman, who works at the NCI. Mark Schiffman, who to many is considered to be a luminary in this area and has published several really important papers in cervical cancer screening, followed over 20,000 women between 1994 and 1996 over a 15-year period and followed them over time using HPV, using a PCR-based assay. Basically what this shows is that over time in women who have type 16, there is a cumulative risk of getting CIN3 or cancer over a 15-year period and below that is type 18, type 31, the other high-risk HPV types, but the bottom line is that type 16 rises to the very top and this is why 16 is so important.

In a Danish study that was published by Susan Kjaer back in JANCI in 2010, which included almost 9,000 women. These women were examined twice, two years apart. They also got HPV testing and genotyping, but again as you can see here in the red curve is that over essentially a 12-year period what you see is almost a straight linear rise in terms of the risk of developing CIN3, particularly with type 16.

There are multiple studies out that look at this, but I think that one study that is really important is the study that was just recently published this year in the American Journal of OB/GYN. This is a study that comes from the Swede screen study in Sweden. This was a huge, randomized controlled trial that basically compared essentially HPV testing plus cytology versus cytology alone. What is really interesting in this paper, and I know that the writing is really small, but the solid black line, the black line on the left, and the key says known persistent status, essentially every single woman in this trial who had a persistent HPV infection basically developed CIN2 or worse – every single woman – and up to this point what we had been telling people is that if you have a woman that is persistently positive for HPV, that lifetime risk of getting CIN2 or CIN3 could be as high as 20 or 25%. What we now know is that it is probably even higher if you are persistently positive for type 16 or any of these other high-risk types.

It would not surprise me at the least over the next five years whether the ASCCP and other groups actually said to people, “Listen, if you have an older woman who is persistently positive, let’s say, for type 16 and that given the lifetime risk of having disease, that that woman may need an excisional procedure. When you actually think about it in women’s health, particularly in the cancer realm, there are very few things in life that carry a risk that high, and that is why HPV persistence in genotyping becomes really relevant because now we are not talking about how do you manage your patients today, but how do you prevent disease in the future down the road, whether it is 1, 5 or 10 years from now?

Clearly what we know is that type 16 is the single most born genotype. Why? It is the worst actor. I have just shown you data regarding that, but also keep in mind that it is the most common and the most prevalent type that we see in the United States and worldwide.

What we also know is that type 31 and 33 are also associated with the pretty high risk of CIN3, which is equivalent to type 18, but right now you do not have the ability to test for type 31 and 33. That is why this talk is about what is coming in the future and what is the next wave in terms of diagnostic testing, and more importantly what we are learning, and you will see this in slides, is that women who are not 16, 18, 31 or 33 positive are at pretty low risk for developing disease. Not all HPV types are actually created equal.

What is the role for genotyping past 16, 18 and 45, what we call the extended genotyping? What you will see here both globally from the state of New Mexico as well as from the Athena trial is in terms of the prevalence or how often you see these genotypes in various studies, looking from 16 going all the way down. Again, 16 is by far the most common type, but the thing to keep in mind as we vaccinate more and more women in this country, we fully anticipate that 16 rates will plummet, right, because we are protecting against 16, but as of right now, 16 is the most common type.

This is what you guys already know and this is what we have taught since the early 2000s basically. If you do a Pap and that Pap is consistent with ASC-US, for the most part in most women, maybe with the exception under 25 years of age, you triage to what? You triage to HPV testing. If it is positive, you go to colpo and if it is negative, you get rescreened, and if you have a Pap that is anything

worse than that, basically, you go straight to colposcopy. What we know is that the rates of CIN2 and CIN3 in that setting is about 10-15%. The question is can we do better than that than what is on this slide right now?

When you look at a different Kaiser study – this is a Kaiser study from Southern California that was also published by Mark Schiffman – basically tested women with hybrid capture 2, he also looked basically at another assay, and it is another assay that is produced by Becton/Dickinson called OncClarity, and this is actually a pretty cool and neat assay that is under FDA review and it would not shock me at all if it became a commonly used assay in the United States, but basically looked at different genotype readouts, looking at three different wells. You can see that 16, 18, and 45 are one well; 33, 58 and 31 are another well; and the third well has other types. I see a stance for internal control and most of these assays now mandate an internal control to make sure that whatever you are testing there is enough cellular material that is there, and basically what you will see here is on the second middle column is basically how common you see these types in the Southern California study; again, what you see is 16 as the most common type, but in the last column gives you an idea of what the three-year, cumulative risk of getting CIN3 or worse is based on these combinations. When you look at it, and this is completely reasonable, there are a ton of numbers of that slide and you are like, "How am I going to remotely remember all those combinations when managing a patient?" That was my criticism five years ago. I do not think it was fair to you all. There is no way that you can remotely do it. This is partly the reason why we have to create that app now to make your lives easier, but you can see the differential risk based on the combinations that are available; but here is the bottom line, and this is really one of the major take-home messages from this lecture. Basically if you have type 16, what we know is that it is markedly different than every other type. It is the black sheep of the family. Okay? It is the most common type based on the study with a prevalence of almost 27%, but it also has the highest risk of getting CIN3 or worse over a three-year period in this study. That is the takeaway. It is how important 16 is in terms of management and screening of women, but when you look at the other types, type 18, 31, 33 and 58, the risk is not nearly as high as 16; it is actually half of that, but the risk is pretty high. Then, this is what we would consider to be the high-risk group ultimately. This is the group that you probably want to do some interrogation and evaluation, whether it is colpo, maybe it is LEEP down the road if they are persistent, that you want to evaluate, and when you look at this and all of these combinations, HPV 16 really counts for over half of the women who are HPV positive have ASC-US.

This combination 51, 39, 68, 35, etcetera, represents a cumulative risk over three years of well less than 3%. This is what we consider to be the low-risk group, so probably this group you could probably just follow over 12 months or even 6 months and not have to do anything else. This group worries me. This is what we call the intermediate risk group. Basically, they have a risk anywhere as high as 4%. The question is what do you do? Do you do colpo? Do you not do colpo? Do you watch them? Do you watch them in six months? Do you have them come back in three months? This is the area that we will ultimately wind up struggling. There is no question on the opposite ends. The highest risk group needs colpo and probably treatment; the lowest risk group can be followed, but what about everyone in between? This is the thing that we are trying to redefine. We are trying to redefine as to how do we best manage this intermediate risk group?

In terms of extended genotyping, now this is what this would look like. If you have an ASC-US Pap, you get HPV testing, and if you are 16, 18, 31, 33 or 58 positive, then you can go straight to colpo. This is different. Again, we have added one additional layer of knowledge and yet complexity to the paradigm in terms of how you would manage these patients, and if they are positive for the other genotypes, they would get rescreened or re-managed in 12 months. You can already see how this gets complicated and gets challenging, but the reason it gets challenging is because we have gained a lot of useful information over the last several years. So, would extended genotyping lead to better clinical care or simply more confusion?

These are the four FDA-approved validated tests that are available in the United States, but the one thing that is completely clear, and this is in all of our guidelines, is that we want providers and labs to use an FDA-approved validated test. Why? Because there are labs in this country that use what we call a "home-brew" assay. It is an assay they develop in their own lab, and yes, it may be what we call analytically validated, but it may not be clinically validated, and so you will see one of the questions, but it would not shock me if less than half this group knew exactly what assay your lab was using. At the end of the day, you may want to look at your report and figure out what assay is being used.

The other thing is, I see this all the time now, there is no role for low-risk testing, and so if you have a lab that is basically doing low-risk testing, they are basically pulling the wool over your eyes. It is completely inappropriate. Again, in terms of what is new in cervical cancer screening there are new colposcopy standards that are coming out, and I will talk about this briefly. Two is that primary HPV screening, is actively being reviewed by the United States Preventive Services Task Force so we should know shortly what their verdict is. Again, that we have guidelines and management of how to manage women that have abnormal vaginal Paps when, unfortunately, people still do Pap smears on women who have had hysterectomies for benign disease. For this group, expect a reiteration in terms of the treatment guidelines in the next two or three years. Thank you very much.

ANNOUNCER CLOSING

Thank you for participating in the Omnia Education CME activity, entitled The Future of Cervical Cancer Screening: HPV Extended Genotyping, Risk Stratification, and Beyond presented by Dr. Warner Huh and recorded live at the Women's Health Annual Visit in Dearborn, Michigan.

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