**Transcript Details**
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The Value of CINtec® *PLUS* Cytology Test in Cervical Cancer Screening

**Announcer:**
Welcome to ReachMD.

This medical industry feature, titled " The Value of CINtec® *PLUS* Cytology Test in Cervical Cancer Screening," is sponsored by Roche.

Here's your host, Jennifer Caudle, MD.

**Dr. Caudle:**
To help assess patients at risk for high-grade HPV-mediated lesions, it may be helpful to have an available biomarker for cervical Pap cytology, as we have in cervical biopsies. So what option is currently available?

I'm Dr. Jennifer Caudle. And joining me to discuss the dual-stain biomarker triage is Dr. Tamera Paczos, who's the Associate Chief Medical Officer at BioReference Health.

Dr. Paczos, welcome to the program.

**Dr. Paczos:**
Thank you for having me to discuss this very important topic.

**Dr. Caudle:**
Well, we're happy that you're here. So, you know, biomarkers have existed for a while, however, most non-pathology clinicians are not as familiar with their significance; p16 became a very important tool for pathologists when it was first introduced in cervical biopsy histology. It acted as a surrogate marker for HPV infection, which is a driving contributor to cervical dysplasia in cancer. To start us off, Dr. Paczos, what was the significance of adding p16 staining to your practice? And how did it change tissue diagnosis in cervical biopsies?

**Dr. Paczos:**
Sure. That's a great question. Just a little background on p16. p16 is the cell cycle regulatory protein that promotes cell cycle arrest. An overexpression of this protein is an indicator of cell cycle dysregulation and transforming HPV infection, putting the patient at risk of harboring a high-grade dysplasia that requires definitive treatment. The introduction of this staining removes some of the subjectivity of histologic interpretation that pathologists can encounter.

When we see dark and diffuse p16 staining, it helps us to identify areas with high-grade HPV-mediated lesions. This can be especially helpful in situations where there are ambiguous lesions that may mimic high-grade disease, such as atrophy.

The use of p16 staining assists us with identifying patients that have high-grade lesions, which can ultimately lead to prompt definitive treatment, such as loop electrosurgical excision procedure or cold-knife cone.

Another really important biomarker that's used in cervical cancer diagnosis is Ki67.

**Dr. Caudle:**
And can you tell us a little more about Ki-67 staining?

**Dr. Paczos:**
Ki67 stain identifies cells that are actively proliferating. Proliferation can occur as part of a reactive and benign process, but it also

occurs in cells undergoing neoplastic transformation.

When we see strong diffuse p16 staining in a biopsy along with increased Ki67 staining, this helps us to identify and confirm high-grade lesions. The utility of p16 and Ki67 immunostaining in biopsies has helped lead to the development of dual staining in cytology specimens.

**Dr. Caudle:**
Now, Dr. Paczos, can you describe the dual-stain cytology test?

**Dr. Paczos:**
Sure, the dual stain biomarker was developed for cytology specimens using both the p16 and Ki67 stains, similar to what was done for biopsies. We can now identify patients at risk for high-grade lesions such as cervical intraepithelial neoplasia 2 or 3, CIN 2 or 3 for short. This can be done in a cytology sample without having to rely solely on morphology. This helps us to facilitate appropriate follow-up and treatment for patients.

**Dr. Caudle:**
So now can you tell us how you plan to utilize the dual-stain CINtec® *PLUS* Cytology test in your practice for cervical screening? And how will it help in your communication of diagnosis with clinicians?

**Dr. Paczos:**
That's a great question. We're planning on offering the CINtec® *PLUS* Cytology test in two different scenarios.

The first is we're planning on offering it for patients who have a Pap smear that is negative for intraepithelial lesion or malignancy, or NILM for short, that also have a positive pooled non-16/18-HPV test. A positive CINtec® *PLUS* result in this case can identify a patient who is at risk for CIN2 or 3, who would otherwise wait for up to a year before getting any follow-up. If CINtec® *PLUS* is done and is positive, they will go to colposcopy immediately.

The second scenario that we're planning on offering CINtec® *PLUS* Cytology in is for patients who have a NILM Pap result and are HPV-16 or HPV-18 positive. We believe that this will help providers risk stratify patients and lead to more timely and appropriate triage treatment and follow-up.

The dual stain as a triage tool helps us to identify those patients with positive high-risk HPV testing that are an increased risk for harboring a precancerous lesion such as CIN2 or 3, and gives a clear indication as to whether the patient needs to go on to colposcopy and possible treatment.

In other words, it reduces ambiguity and reliance on morphology and provides clear answers to clinicians.

An important point is that the interpretation of Pap cytology specimens can be subjective, especially in early or late lesions, as well as when there are very few abnormal cells present.

CINtec® *PLUS* Cytology reduces the chance of us missing these lesions when looking at a Pap smear and removes reliance on morphology alone.

CINtec® *PLUS* is considered positive even if we identify only one abnormal dual stain cell. A recent study showed that by more clearly identifying women at risk of developing cervical cancer, CINtec® *PLUS* Cytology provides superior immediate and long-term risk stratification compared with Pap cytology.

**Dr. Caudle:**
Thank you for that. And for those of you who are just tuning in, you're listening to ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Tamera Paczos about dual stain biomarkers in cervical cancer screening.

Dr. Paczos, we just spoke about p16 and the development of a triage test. But now let's shift over to the evidence that prompted you to incorporate this testing and modality into your practice. Looking at the improving primary screening and colposcopy triage, or IMPACT trial, Dr. Paczos, what were the significant points from this study that prompted your adoption of the dual stain test to your lab and protocol?

**Dr. Paczos:**
Of course. After reviewing the IMPACT trial results, what really hit home for me was the increased sensitivity and specificity compared with cytology-based testing to identify patients at risk of having a high-grade disease.

The results of the trial demonstrated decreased reliance on morphology and cytology. And as a pathologist, this helps to reassure me

that I won't miss a potential high-grade cell. For a clinician, it gets patients to treatment quicker if they do have disease, and it prevents unnecessary colposcopies and biopsies if they don't.

The study also demonstrated that in a patient with a negative dual stain, the risk of that patient harboring a high-grade lesion was significantly lower when compared to cytology-based testing, such as co-testing, or cytology alone. Basically, the negative predictive value is very impressive.

In the end, the sufficient triage puts less burden on our overtaxed healthcare system and leads to fewer colposcopies, which is an unpleasant procedure for a patient to endure if they don't need it.

**Dr. Caudle:**
That's very helpful. So, to reiterate, can you tell us again, uh, what the IMPACT trial shows?

**Dr. Paczos:**
The IMPACT trial demonstrates that CINtec® *PLUS* Cytology is highly sensitive and catches more at-risk women sooner, potentially reducing disease progression in individuals otherwise sent home for later follow-up. Negative CINtec® *PLUS* Cytology more accurately identifies a patient at low risk, reducing the need for follow-up appointments and unnecessary invasive procedures. An added benefit is that CINtec® *PLUS* Cytology can be performed using the same patient samples collected for HPV screening and their Pap smear cytology, meaning that they don't need any additional follow-up sampling.

**Dr. Caudle:**
Yes, exactly. And thank you for that insight, Dr. Paczos. Now let's move on to some examples. Can you walk us through a case scenario?

**Dr. Paczos:**
Sure a patient that presents to their provider, has a Pap smear done and the result is NILM, or normal, but they have an HPV test that's positive for 12 other pooled high-risk HPV. In this scenario, the patient is concerned even though their Pap smear is normal, but they have a positive HPV result. A dual stain test was performed and was positive. This patient returned for a colposcopy and biopsies, and they revealed CIN2. They were referred for definitive treatment. If the CINtec® *PLUS* Cytology was not performed, they may have waited up to a year prior to being seen again.

The bottom line is CINtec® *PLUS* Cytology dual staining helps us manage the NILM HPV positive patients in a risk-based fashion and helps direct healthcare resources to those who truly need them.

**Dr. Caudle:**
Well, thank you for that. It's a great way to round out our discussion on dual stain biomarker triage. I'd like to thank my guest, Dr. Tamera Paczos, for helping us better understand the value of the CINtec® *PLUS* Cytology test in cervical cancer screening. Dr. Paczos, it was great speaking with you today.

**Dr. Paczos:**
Thank you for having me here today.

**Dr. Caudle:**
Thank you. I'm your host, Dr. Jennifer Caudle, and thank you for listening.

**Announcer:**
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