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Advancements in Cervical Cancer & the Role of Biomarkers

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Advancements in Cervical Cancer & the Role of Biomarkers” is sponsored by Roche Diagnostics.

This program is intended for physicians. Here’s your host, Dr. Charles Turck.

Dr. Turck:
Cervical cancer is the fourth most common cancer in women worldwide, which makes it essential for us to keep ahead of advances in its prevention and the availability of new and approved testing modalities. The Pap test has played a key role in reducing cervical cancer since its introduction in the 1940s, but like any test, it isn’t without its limitations (Safaeian et al. PMID 18061867). But a new cytology-based test approved for use in the US has the potential to change the way we think about cervical cancer screening today.

This is ReachMD. I’m Dr. Charles Turck. Joining me today to discuss the recent advancements in cervical cancer screening is Dr. Lee Shulman, the Anna Ross Lapham Professor in Obstetrics and Gynecology in the Division of Clinical Genetics at the Feinberg School of Medicine at Northwestern University in Chicago, Illinois.

Dr. Shulman, thanks for being here today.

Dr. Shulman:
Thank you. It’s great to be here today with you.

Dr. Turck:
Now to start, Dr. Shulman, would you review for us the principles that help guide effective cervical cancer screening programs?

Dr. Shulman:
Well, the goal of cervical cancer screening is actually to identify precancerous cervical disease early and with certainty, before that disease develops into actual cervical cancer.

Successful cervical cancer screening programs are based on two fundamental principles:
One is centered around risk stratification, which is identifying who is safe from developing disease, and who is at risk of developing precancerous cervical disease. In order to answer the question about risk, a test is required with high sensitivity to RULE OUT disease.

The second is around disease stratification, which means identifying who would actually benefit from intervention. In order to answer the question about disease, a test is required with high specificity to RULE IN who has the disease. This provides higher certainty about who may have disease and as a result drives the intervention protocol.

The mix of risk stratification and disease stratification is what we’re trying to achieve with cervical cancer screening. The most common test associated with cervical cancer screening is the pap test which has been the “gold standard” for decades. It was a major reason for the reduction of cervical cancer morbidity and mortality upon its introduction in the 1940s.

We learned over time that when used alone, to assess women for precancerous cervical disease, the pap had considerable limitations; it is based on subjective interpretation of morphology of cells and can lead to missing disease.

In 1999, the FDA approved the first HPV test that introduced a more sensitive and specific screening algorithm. Over time, professional societies recognized the utility of co-testing which is using both pap & HPV test results to guide patient management. What we are

seeing now is that assessing samples for high-risk HPV is playing an even more important role in cervical cancer screening with the recent clearance by the FDA of Primary HPV screening, a screening test that has been shown to be a highly effective tool for identifying women at high risk for progressing to precancerous cervical disease as well as those women who are least likely to progress to precancerous cervical disease.

Dr. Turck:
Let's focus on that role for a moment. How has HPV testing become so important in cervical cancer screening?

Dr. Shulman:
Well, we now know that HPV is the cause of >99% of cervical cancers. Large cervical cancer studies such as ATHENA have shown that HPV testing as a screening method is significantly more sensitive than Pap at detecting high grade cervical dysplasia. HPV testing increased detection of CIN3 or greater disease by 72% over PAP cytology alone and these findings are consistent with other trials findings.

Dr. Turck:
But I take it that, based on what you mentioned earlier, sensitivity is only one side of the coin here, especially with respect to triaging patients. What are your thoughts on that?

Dr. Shulman:
Although HPV testing is highly sensitive at identifying women at risk, 70-90% of HPV infections will eventually clear so most high-risk HPV positive woman will likely not have cervical pre-cancer conditions or cervical cancer. We thus need a triage test to help determine which HPV positive women are at the greatest risk for cervical disease and would benefit most from colposcopy.

Dr. Turck:
For those just tuning in, this is ReachMD. I'm your host, Dr. Charles Turck and today I'm speaking with Dr. Lee Shulman about the current understanding of and advances in screening for cervical cancer.

So Dr. Shulman, coming back to the testing methodologies for cervical cancer screening, what are the gaps that we need to keep top-of-mind?

Dr. Shulman:
The fact is that unclear or inconclusive screening test results create challenges and not every HPV-positive woman will develop cervical cancer. Uncertainty can lead to over- or under-treatment and both come with consequences.

Overtreatment may result in colposcopy and biopsies that may not be necessary. While colposcopy is a common and relatively safe procedure, evidence suggests that undergoing colposcopy after an abnormal cervical cancer screening result can have negative impact upon women's psychological, physical health and sexual health and well-being.(REF:ttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC6086061/)

Consequences of under-treatment are missed diagnoses with progression leading to increased costs and undue suffering because more aggressive treatment was delayed.

An ongoing unmet need in cervical cancer screening has been to have a reliable method that can indicate the likelihood of the ongoing process of oncogenic transformation. This is where biomarkers, traditionally reserved for disease confirmation, come into play.

Dr. Turck:
So, let's consider biomarkers in more detail, then. How do you look at biomarkers in the context of cervical cancer screening?

Dr. Shulman:
Well a biomarker is a defined characteristic that is a measurable or objective indicator of either normal biological processes, pathogenic processes, or responses to an exposure or intervention. Objective biomarkers provide more definitive results of precancer and are the next evolution in cervical cancer screening. …Biomarkers help avoid over and under treatment and help manage patients in a timely manner to prevent the development of cervical cancer. (REF: FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US), www.ncbi.nlm.nih.gov/books/NBK326791/ (2016, accessed 22 September 2017).

CINtec PLUS Cytology is a biomarker-based cytology test that was FDA cleared in March 2020 to be used as a triage in both co-testing and the HPV Primary Screening algorithms. The test uses a combination of two biomarkers – P16 and Ki-67 – and it represents a step forward in using molecular markers to more accurately detect transforming cells. P16 and ki-67 are mutually exclusive proteins in a normal cell. Presence of dual stained cells for both p16 and ki-67 indicate cell-cycle deregulation that is a hallmark of transforming

persistent HPV infections.

Women who have an HPV infection that show signs of cellular transformation based on the abnormal co-expression of biomarkers p16 and ki-67 are at the highest risk for high grade cervical dysplasia and should be referred for colposcopic evaluation. A woman with a negative (CINtec PLUS Cytology) result can return for follow up screening to allow her body time to clear the HPV infection.

CINtec PLUS cytology therefore focuses on objective detection of molecular driver events behind the HPV transforming infection, rather than the more subjective morphologic manifestation of high-grade cytology.

Dr. Turck:
And just as a point of clarification, Dr. Shulman: how is this test run compared to liquid-based or PAP cytology?

Dr. Shulman:
The CINtec PLUS Cytology test is run from the same collection as liquid-based samples for HPV and PAP cytology so the test requires no additional steps for the healthcare provider.

Dr. Turck:
An before we close, Dr. Shulman, do have any final comments?

Dr. Shulman:
CINtec Plus cytology is a new approach to cervical cancer screening and has the potential to provide an even more sensitive and specific screening assay that will more accurately assign women to cervical disease risk categories and thus further improve the cervical disease screening process.

We've truly come a long way from the landmark work of Professor Papanicolau and the erstwhile "Pap smear." Our ability to weave together molecular biology with cytopathology and biomarker analysis allows us to combine technologies to improve the clinical care that we provide in our offices.

Dr. Turck:
Well these are all great considerations as we come to the end of today's program.

I want to thank my guest, Dr. Lee Shulman, for helping us better understand the diagnostic landscape and unmet needs for cervical cancer screening programs, and how novel testing methods are changing the way we think about cervical cancer prevention going forward.

Dr. Shulman it was great speaking with you today.

Dr. Shulman:
And same here. Thank you very much.

Announcer:
This program was sponsored by Roche Diagnostics 'doing now what patients need next.' If you missed any part of this discussion, visit ReachMD.com/IndustryFeature. This is ReachMD. Be part of the knowledge.