AACC Guidance Document on Cervical Cancer Detection: Screening, Surveillance, and Diagnosis

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Guests: Dr. Yusheng Zhu is the current AACC Academy President and a Professor at the Pennsylvania University Hershey Medical Center. Dr. Sarah Feldman is the Medical Director of the Ambulatory Gynecologic Oncology Clinic at Brigham and Women's Hospital and an Associate Professor at Harvard Medical School.

Randye Kaye: Hello, and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye. The CDC estimates that about 13,000 new cases of cervical cancer are diagnosed each year in the United States. A large majority of cases are known to be caused by long lasting infection with certain types of human papillomavirus or HPV. While many professional organizations offer guidelines for cervical cancer screening, there are several different approaches to cervical cancer testing and the test of choice may differ depending on the indication for testing and the patient's unique risk factors. The March 2023 issue of *JALM* features the AACC Academy's latest guidance document on cervical cancer detection, screening, surveillance, and diagnosis.

The guidance document discusses currently available cervical cancer screening tests and testing strategies, current screening guidelines, and risk-based management guidelines. The authors also provide a reporting template for HPV and cervical cancer detection to facilitate optimal interpretation of test results and clinical decision-making. Today, we're joined by two of the guidance document's authors. Dr. Yusheng Zhu is the current AACC Academy President and he chaired the Writing Committee. Dr. Zhu is a Professor of Pathology and Laboratory Medicine and Pharmacology at the Pennsylvania University Hershey Medical Center. We're also joined by Dr. Sarah Feldman, who is the Medical Director of the Ambulatory Gynecologic Oncology Clinic at Brigham and Women's Hospital and an Associate Professor at Harvard Medical School. Dr. Zhu and Feldman, welcome. Why did the AAC Academy decide to publish a new guidance document on this topic of cervical cancer detection? Dr. Zhu?

Yusheng Zhu: Currently, there are multiple strategies for cervical cancer screening. For example, high risk HPV, primary screening, co-testing, including both HPV and the cervical cytology testing, and the cytology testing alone. Also, both American

Cancer Society and the United States Preventative Services Task Force have published new guidelines on cervical cancer screening and they have some differences. In addition, American Society for Colposcopy and Cervical Pathology has published new risk-based management consensus guidelines for patients with abnormal cervical cancer screening and cancer precursors for surveillance. To help clinical laboratories understand various strategies for cervical cancer screening, differences in these guidelines, as well as differentiate screening, risk based surveillance, and diagnosis of cervical cancer, the AACC Academy decided to publish this comprehensive guidance document.

Randye Kaye: Thank you. Can you share with our audience the process of how this guidance document was developed?

Yusheng Zhu: Absolutely. First of all, we assembled a great team, including members with different expertise, to work on this guidance document. The team consists of clinical chemists, gynecological oncologists, molecular pathologists, cytopathologists and histopathologists. They are experts in cervical cancer research, diagnosis, and management. Then, the team selected most important questions about cervical cancer screening, surveillance, and diagnosis, and conducted a thorough literature search to include the most recent publications and guidelines from major professional organizations. The guidance document was reviewed by the AACC Academy council and then went through the process of a public comment. The final document was approved by the AACC Board of Directors prior to publication.

Randye Kaye: According to this guidance document, cervical cancer screening options include screening for human papillomavirus or HPV, cervical cytology also known as the PAP test, and then co-testing, which uses both of these screening methods simultaneously. Dr. Zhu, could you tell us how these different strategies impact clinical laboratories? And then, Dr. Feldman, could you comment on how they impact clinical care?

Yusheng Zhu: This is a great question. Clinical laboratorians should discuss these options with the clinical staff who are responsible for screening, surveillance, and diagnosis of cervical cancer, to select an appropriate strategy based on available instruments and expertise of clinical laboratories. For example, only two HPV assays are approved by the FDA for HPV primary screening at this moment. If an institution decides to use HPV primary screening strategy, the clinical lab should make sure that the instruments for these assays are available. Clinical laboratorians should also closely work with clinical staff and IT department to determine how to report the results of cervical cancer testing.

In this guidance document, we proposed an ideal laboratory report template to group all necessary information on cervical cancer detection together in patients' charts. The information includes patient identification, indication for the tests, such as screening, surveillance, or diagnostic workup of symptomatic patients, clinical history of the patients, and the prior results provided by the ordering clinicians. So the lab has all necessary patient information. If a request is for screening, the ordering clinician will indicate the strategy of screening, i.e., primary HPV screening, cytology alone, or co-testing. The lab will report all results of the tests ordered by the clinician together in patients' charts, so it is easier for clinicians to review and interpret all results and manage their patients more effectively.

Randye Kaye: Dr. Feldman?

Sarah Feldman: Yeah. Thank you, Dr. Zhu for an excellent summary of the issues and concerns. This is a complicated time in terms of cervical cancer screening in the United States as we don't have a national standard, and thus, labs are doing many different things. And what that means for clinicians is they may not be able to access the most up to date screening modalities, such as an FDA approved primary HPV test, if their lab doesn't have it available. My understanding is that it's often very expensive and complex logistically to transition to the FDA approved technology, so this is not available in most labs yet in the United States. However, it may disproportionately affect certain populations and increase disparities. Furthermore, clinicians may not know exactly how to manage patients under the new screening paradigm, which may result in confusion between the laboratories and the providers. For example, the order of reporting certain results may change, such as reporting an HPV before the reflex cytology, and for those providers and patients who are used to the cytology being the primary test with either a co-test with HPV or a reflex to HPV, that may confuse patients and providers. They may not understand that the cytology is a reflex and may not come at the same time, and also that their management has to wait for that second test result.

Randye Kaye: All right, thank you. So, Dr. Feldman, what kind of changes do you anticipate that we might see in cervical cancer screening over the next few years?

Sarah Feldman: Well, the first one is that, as Dr. Zhu mentioned, the American Cancer Society has proposed that primary HPV testing with reflex to genotyping and cytology be the baseline test. We do not yet know what the US Preventive Services Task Force will recommend in their next recommendations, although we anticipate also primary HPV testing. So I imagine that eventually we will see a big movement towards a primary HPV test with a reflex to genotyping and cytology. Second of all,

the FDA is currently considering self-testing. Self-testing means that the patient would test for HPV on their own without a clinician exam, and then they would be triaged.

Again, that would be a test for HPV and they would be triaged to cytology and/or subsequent testing as needed. It has not yet been FDA approved in the United States, but it's being used in many parts of the world and has been shown to increase access to marginalized populations who may not feel comfortable or may live too far to come in for routine clinician care. The next thing that we may see eventually, and I don't think this is coming soon, but eventually, will be point-of-care testing. What that means is that the test itself, similar to a COVID test, the patient may be able to actually get the result of the HPV test at home. Of course, before we do that, we'll need to have a whole system for what to do with that result and how to create a registry of all the patients who have been offered that type of testing and what the results are, but that would be a dramatic change for laboratories, obviously, as it will take the laboratory out of that initial screening.

And that again has started in other parts of the world, not yet in the United States. And then, of course, on the cytology aspect, there is going to be reflex testing, I believe that will become endorsed by the large associations relatively soon, such as stool stain, more complex genotyping beyond 16 and 18, things like that.

Randye Kaye: All right, thank you. Certainly a lot of change ahead. Now, clinical laboratory tests may be used for different clinical indications, and that goes for cervical cancer detection methods as well. So why is it important to differentiate the cervical cancer testing methods used for screening, risk-based surveillance, and diagnosis?

Sarah Feldman: Well, the laboratory test is actually the same, but how the result is used may differ. So, risk assessment depends on both current and prior test results, and that includes both the HPV, the cytology, and the histology results. A clinician ideally needs to have all of those reported together and if the patient has had all their results in the same laboratory, the easiest way to do that is to give that report with the most recent results on the same report. In order for a clinician to recommend the next steps, they essentially need all those results presented together. But also for the lab. If the patient, for example, has a history of a high grade or HPV 16, which would be a surveillance patient, or if she has a large mass concerning for cervical cancer, so that would be a diagnostic indication. The lab then knows that the concern that this current test is abnormal is higher and that may affect how that slide is evaluated and what stains are used, et cetera.

Randye Kaye: All right, thank you. So my final question. You're both obviously esteemed experts in these areas. Starting with you, Dr. Zhu, can you talk about where your own research in this field is going?

Yusheng Zhu: Currently, the test for HPV screening and cytology testing requires expensive instruments and professionals with special expertise. However, most of the cervical cancer deaths occur in low resource countries and regions where these instruments and expertise are unavailable. Specimens have to be sent to central laboratories for testing. Because of limited access to these tests, high cost, long turnaround time, and possible loss of patient follow-up, point-of-care HPV tests that are easy to use, with low cost, and can be performed in clinics are highly desirable in these regions. I'm working with other researchers trying to develop rapid, low cost, sensitive, and accurate point-of-care HPV testing device for cervical cancer screening in low resource regions without expensive instruments and laboratory expertise.

Randye Kaye: Thank you, Dr. Feldman?

Sarah Feldman: Well, first, I have to say, wow, I'm so excited that that's what Dr. Zhu is working on and I hope I can work with him in the future. My answer is very similar, actually. Cervical cancer is a preventable disease. However, it disproportionately affects certain groups, often due to inadequate screening, lack of appropriate management of pre cancer solutions, and to Dr. Zhu's point, this disproportionately affects women in low resource areas, both around the world, but also even within the United States in certain types of communities. So most of my research focuses on understanding how to improve access to and compliance with care to prevent cervical cancer. I think, as Dr. Zhu said, the safe, effective point-of-care testing is going to be extremely important but in addition to that, we're going to need systems to, once the test is abnormal, manage those abnormalities to actually prevent cancer, and that is also where my interests lie.

Randye Kaye: Thank you so much. Thank you both for joining us today.

Sarah Feldman: Right, thank you.

Yusheng Zhu: Thank you, Randye.

Randye Kaye: That was Drs. Yusheng Zhu and Sarah Feldman describing the *JALM* article, "AACC Guidance Document on Cervical Cancer Detection: Screening, Surveillance, and Diagnosis." Thanks for tuning in to this episode of *JALM* Talk. See you next time and don't forget to submit something for us to talk about.