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REVIEW ARTICLE

Controversies in Pathology

Should screening for cervical cancer go to primary human papillomavirus testing and eliminate cytology?

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This review will systematically highlight the pros and cons of cervical cancer screening with HPV (human papillomavirus) testing and cytological methods (Papanicolaou (Pap) test). When comparing the screening modalities, various facets will be addressed, such as cost effectiveness, and harms and benefits across different demographics and age groups. It is important to note that due to the expansive variance in material costs, practices, and resource availability across different geographical regions, these comparisons are far from straight forward, and ultimately make it challenging to render definitive global recommendations. Thus, the intent of this review is to highlight some of the differences in difference cervical cancer screening modalities that can help one to choose an optimal screening method in their specific situation.

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INTRODUCTION

In the mid-1800s, when Irish physician Dr. Walter Hayle Walsh showed that cancerous cells could be seen by microscopy, the true far reaching effect of this discovery on cancer screening and prevention was unimaginable[1]. Over a century later, this breakthrough aided Dr. George Papanicolaou, a researcher and physician of Greek origin, in discovering the first cervical screening test "the cervicovaginal smear", which was then first published in 1940 and became known as the "Papanicolaou (Pap) smear" or "Pap test". Around the same time, similar approaches to cervical cancer screening were being investigated by Constantin Daniel, a professor of Gynecology and Obstetrics, who used a smear technique designed by Aurel Babes, a pathologist and researcher in Romania, to diagnose cervical cancer. Although similar, Babes' method differed from the Papanicolaou method with respect to method of sampling, fixation, and staining in that it used smaller histopathological studies with air-dried smears stained with Giemsa[2]. The process has since evolved and expanded with cervical cancer screening modalities becoming much more sophisticated[3]. For instance, in the mid-1990s, liquid based cytology was shown to have better slide quality than the conventional method and provided other advantages, which allowed it to almost entirely replace conventional smears[4]. Later, it was discovered that human papillomavirus (HPV) was a viral etiologic factor involved with cervical cancer, which initiated efforts to determine ways to detect HPV infections in the cervix. Then, in the past 10 years, we have seen the emergence of an HPV (human papillomavirus) vaccine and other changes to decrease the incidence of cervical cancer even further. These developments in the story of cervical cancer screening are summarized in Fig. 1.

Although we have come a long way since Dr. Papanicolaou's initial procedure in 1920, cervical cancer remains a major cause of morbidity and mortality among adult women. In fact, it has become the fourth leading cause of mortality and incidence among adult women around the world. With as many as 570,000 cases reported in 2018, leading to nearly 270,000 deaths[5]. Developing countries, including middle and low-income populations, comprise around 85% of those worldwide deaths from cervical cancer. Thus, there has been interest in trying to improve the cervical cancer screening process overall, as well as making it more easily accessible and effectively implemented in low-resource settings, all while maintaining the goal of timely detection of cervical precancer to prevent the development of invasive cervical cancer[6].

Dr. Papanicolaou's collaboration with gynecological pathologist Dr. Herbert in 1940 and their publication on the Pap smear paved the way for pathologists to understand the morphological changes in the cervical mucosa. This has since led to a tremendous drop in cases of cervical cancer mortality and the incidence of cervical cancer. American women alone, have seen an astounding 80% decline in cervical cancer related deaths from 1930 to 2012[3]. A study conducted by Dr. Lees in 2016 shows that the simple implementation of routine cervical cytology screening can have a dramatic impact on the reduction in mortality and incidence rates[3]. Most notably, from 1950 to 1970, her findings indicated a significant 3% annual decline in some areas, which highlights the significance of the screening process. This study, amongst many others, has led to the vast progression of the existing cervical cancer screening guidelines, as well as the emergence of new screening strategies over the past 15 years[3].

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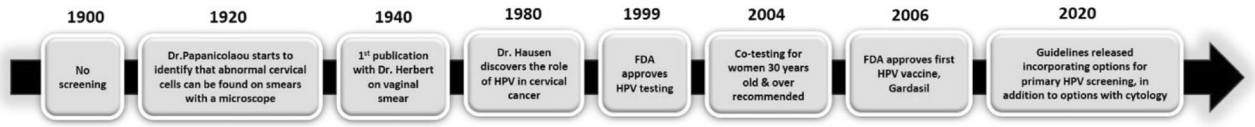

Fig. 1 Timeline of major events in cervical cancer screening. A timeline illustrating some of the major events in cervical cancer screening, starting with a lack of screening in the early 1900s, to the early research leading to the discovery that a microscope could be used to detect abnormal cervical cells on smears (Pap smear/test). Then in the late 1900's was the discovery of HPV having a role in the development of cervical cancer and FDA approval of HPV testing on Pap tests. Subsequently, there was an FDA approval of HPV vaccines and new guidelines incorporating options for primary HPV screening.

Table 1. Screening guidelines of 2020 American Cancer Society (ACS)[10] vs United States Preventive Services Taskforce (USPSTF) endorsed by American Society for Coloscopy and Cervical Pathology (ASCCP)[11].

Age	**2020 ACS**
Aged < 25 year	No screening
Aged 25–65 year	Primary HPV test alone every 5 year (preferred) or, in case HPV testing is limited or not available, other options are like (Co-testing every 5 years OR Cytology alone evey 3 years) are acceptable
Aged > 65 year	Discontinue screening if adequate negative prior screening
	Without documentation of prior screening, it should continue screening until criteria for cessation are met
After hysterectomy	Individuals without a cervix and without a history of CIN2 or a more severe diagnosis in the past 25 year or cervical cancer ever should not be screened
Age	**2019 ASCCP**
Aged < 21 year	No screening
Aged 21–29 year	Cytology alone every 3 years
Aged 30–65 year	Either one of these methods: (1) Cytology every 3 years (2) hrHPV testing every 5 years (3) Co-testing (hrHPV testing + Cytology) every 5 years
After 65 years	No screening after adequate negative previous results
After hysterectomy	Individuals without a cervix and without a history of CIN2 or a more severe diagnosis in the past 25 year or cervical cancer ever should not be screened

Forty years after the initial publication on the Pap test, the next great breakthrough in this field was made when HPV was discovered as the causative agent of the majority of cervical cancer. It was found that HPV is a small nonenveloped DNA virus with more than 200 types within the Papillomaviridae family. Of the many types, only a small subset was identified to be the most oncogenic (including high-risk HPV types 16 and 18) and estimated to be the cause of around 97% of cervical cancer cases. However, there are other rare and poorly characterized viral types that likely cause a small percentage of high-grade dysplasias and cancers, which may partly explain the reason for false negative HPV tests. It is no surprise that such a significant discovery has had such a significant impact on cervical cancer screening and made us reappraise how to best perform cervical cancer screening[1,7,8].

Initial recommendations for cervical cancer screening were for women to have an annual Pap smear examination to look for cellular changes associated with squamous cell abnormalities of the cervix, and this 1 year interval was created prior to completely understanding the role of HPV in cervical cancer. The screening was performed as conventional Pap smears in the early years, and then transitioned to liquid based cytology around 1996, given that liquid based techniques improved cellular visualization and minimized obscuring factors. By 2012, having developed a greater understanding of the HPV virus, the screening recommendations were much more clearly defined. By then, studies had shown that there was no clear indication for rationally screening women younger than 21 years old, since most of the HPV infections will be transient or take many years between initial infection and the development of invasive cancer. The incidence of cervical cancer in this age group is also low (0.1% of all cervical cancer cases)[9]. However, early screening in young patients could be reasonably initiated by their gynecologist or provider for certain candidates who are deemed high-risk, including those who have early sexual history or are immunocompromised. These screening guidelines were shaped by our enhanced understanding of the nature of the HPV infection over the years, which has shown that most HPV infections will take many years before reaching an invasive cancer phase; thus, exposing this young age group to unnecessary tests cause needless stress and potential harm[3,7,8].

Even though the updated American Cancer Society (ACS) guidelines in 2020 recommend initiation of screening at age 25 years old and favors HPV testing for primary screening[10], there have been other groups that have advocated for a different approach. The American College of Obstetricians and Gynecologists (ACOG), and the American Society for Colposcopy and Cervical Pathology (ASCCP), still endorse the 2018 screening recommendations made by the U.S. Preventive Services Taskforce (USPSTF)[11], which states the following: women are recommended to start screening at the age of 21 years old if they are immunocompetent and asymptomatic. Between 21 to 29 years of age, it is recommended that women should be cytologically screened every 3 years. Finally, for women between 30 to 65 years of age, it is recommended to be screened using one of the three following methods: once every 5 years with cytology and high-risk HPV testing (so called "co-testing"), once every 3 years with cytology alone, or once every 5 years with high-risk HPV testing alone[7,8]. (Table 1) Women older than 65 years can discontinue screening if there is adequate history of negative screening results (three consecutive cytology results or two consecutive co-testing results within the past 10 years before discontinuing screening, with the most recent test done within last 5 years), also women who went through a total hysterectomy and have no history of a high-grade cervical lesion or cancer can

cease screening[3,7,8]. It is important to recognize, that although these are the approaches endorsed in the U.S., other countries approach screening differently. For example, in the Netherlands, it is not recommended to start cervical cancer screening until the age of 30 years old due to the perceived limited impact in younger women, compared to the substantially higher benefit seen with screening in older women.

Despite the introduction of a preventive HPV vaccine, the vaccine accessibility is still highly variable based on socio-economic and geographic factors, and full vaccination takes a period of years, which highlights why screening remains important to diagnose any cervical changes. Thus, the current American Cancer Society guidelines recommend that vaccinated individuals still follow age-specific screening recommendations similar to that of unvaccinated individuals[5] (TABLE 1).

In addition to the HPV vaccine, there have been other developments in the HPV molecular testing process that have recently began to impact screening. This new screening strategy focused on the detection of high-risk HPV was developed by the United States Food and Drug Administration (FDA) in 1999 to reduce the high variability observed within the cytology screening test results[3]. Given that 2 (HPV16 and HPV18) of the 14 high-risk HPV (hr HPV) genotypes have been linked to the overwhelming majority of all reported cases, and interact with the viral proteins E6 and E7 contributing to unregulated cell growth, there has been developments in testing allowing for the detection of these HPV types to enhance the sensitivity of cervical cancer screening, and overcome the inherent variability in the interpretation of the screening results by Pap test[3].

In this article, the different cervical cancer screening modalities are discussed, with a review of the advantages and disadvantages of each, in order to better understand all the cervical cancer screening options. These findings are also summarized in Table 2.

CYTOLOGY SCREENING

Since Dr. Papanicolaou's invention of the Pap smear, cervical cytology has established itself as an effective method for detecting cervical lesions by routine microscopy. The process occurs through fixing the cervical cells on a slide to be viewed under a conventional light microscope and use of the Papanicolaou stain allows for visualization of the cell's morphology by observing the nucleus and its cytoplasm[1]. Studies showed that conventional Pap smears have helped dramatically in reducing the incidence and mortality rates of cervical cancer. Moreover, the International Agency for Research on Cancer (IARC) revealed that 80% of invasive cervical cancer can be reduced with the Pap smear. Although the test was devised to detect squamous abnormalities of the cervix, there are additional benefits, such as the detection of infectious etiologies and glandular lesions arising from the cervix or endometrium, in addition to rare cases of metastatic carcinomas. Despite its widespread use since 1940s, there are some limitations to this method that led to further developments and attempts to improve cervical cancer screening even more[1].

In mid-1990s, liquid based cytology was approved by the FDA and introduced as an alternative method to resolve the limitations of the conventional Pap smear. The liquid based method still involves collection of a cervical sample, but instead of being spread on a slide in an inconsistent fashion that was operator dependent, the sample gets rinsed in a transport medium vial to be processed in the laboratory, during which any obscuring material, such as blood or mucus, gets separated from the sample, and the sample is then deposited in a well-defined circular area on a microscope slide for enhanced visualization and screening[12]. This optimized technique reduced the number of unacceptable smears that required repeat testing due to poor cell preservation or preparation, or due to blood/mucus obscuring the slides. This, in turn, decreased the amount of time required (around 20 min) for the Pap test to be performed and reduced the number of insufficiently cellular or poorly fixed cases that could result in false negatives and false positives. Lastly, it allowed pathologists to use the same sample for HPV triage if needed, since conventional Pap tests only used small part of the sample taken from the patient to be transferred on the slide[1,12]. Studies have also shown that using the same vial for liquid based cytology and HPV testing have resulted in better detection rates of cervical abnormalities than conventional Pap tests, because of its immediate wet fixation of the sample, as well as giving the opportunity to do molecular testing on the same vial from the same visit, minimizing the need for a repeat procedure[13].

The benefits of liquid based cytology have been shown in the ease of screening and ability to improve the quality of cervical cancer screening given the high cervical intraepithelial neoplasia (CIN) detection rate over conventional Pap tests, and the increased sensitivity and increased detection of significant abnormalities[12,14,15], Although liquid based cytology does offer benefits, it is important to realize that some studies and meta-analyses have shown a decreased or only comparable sensitivity and specificity with conventional Pap smears without significant improvement[16,17]. Other noteworthy advantages of cytological screening with liquid based methods is the ability to quantitatively determine during the microscope evaluation if there is sufficient cellularity and transformation zone sampling to indicate an adequate sample. This is particularly important in the setting of unsatisfactory Pap tests with HPV ordered regardless, given that there are settings where the HPV testing platforms are not FDA approved and have no internal control for squamous cellularity. In these scenarios, suggesting a repeat Pap test, opposed to assuming the HPV result is informative and truly negative may be warranted. Other advantages that cytology screening provides is the ability to detect infections, metastases, and unique tumors with characteristic immunophenotype (e.g., neuroendocrine carcinomas). Non-HPV related lesions are also able to be detected, such as endometrial cells (benign or atypical), and non-HPV related adenocarcinomas or other tumors of the gynecological tract. Despite the intent of the Pap test to detect cervical cancer, these are added benefits of the Pap test that would potentially get missed with a screening modality that abandons routine morphologic review.

Despite the improvement of cervical cytology performance using liquid based techniques, the cost of highly trained pathologists, the subjective morphological interpretations by cytologists, the increased number of costly screenings required in shorter intervals (every 3 years) due to the compromised sensitivity with uncertainty for false negative results, caused a reconsideration of screening that relies entirely on cytological methods[1]. In some regions of the world, where Pap tests have a greater chance of being falsely negative, the effect can be postponement of timely necessary treatments which can be detrimental to the patients. This raises the issue that perhaps optimizing the Pap test, opposed to abandoning it, will provide a better approach. This may include centralizing the interpretation of Pap tests or requiring strict quality control metrics, as done in places such as Europe, that may maximize Pap test performance. The shift to increasing utilization of the HPV vaccination was another major factor that reinforced the decreased reliability on cytological methods, as the increasing vaccinated population decreases the incidence of high-grade lesions, which diminishes the advantages of utilizing a high specificity test like the Pap test.

HPV SCREENING

The discovery of HPV as a viral infectious agent linked to cervical cancer enabled the development of sensitive HPV screening tests for the detection of cervical cancer. HPV testing started as a reflex

Table 2. Comparison of advantages and disadvantages for different screening modalities for cervical cancer.

Screening	Pros	Cons
Conventional Cytology	• First test to decrease incidence of cervical cancer. • Easy to prepare without complex equipment.	• Time consuming (stain procedure takes around 20 min). • Smearing is vulnerable to obscuration by blood and mucus, and imperfect fixation. • Quality of preparation is operator dependent. • Interpretation by well-trained cytologists can be subjective. • Broad range of sensitivity (30–87%), lower than other testing. • Short intervals between screenings, due to potential false negative results, necessitating more visits
Liquid based Cytology	• Developed to address the shortcomings of the conventional Pap smear and shown to have a higher sensitivity than conventional Pap tests in some studies. • Can decrease the proportion of inadequate smears. • Enables a triage test (e.g., an HPV test) to be performed on the same material and same vial as part of co-testing (see below). • Reduced numbers of unsatisfactory Pap tests. • Easier to screen. • Better visualization of squamous cells with a more even cellular preparation to assess adequacy of cellularity and morphology.	• Some studies have shown that the sensitivity is less than or comparable to that of the conventional Pap test. • Interpretation by well-trained cytologists can be subjective. • Sensitivity is still not optimal, with high numbers of borderline results that require further testing, and raise uncertainty for false negative results. • Requires high-quality diagnostic facilities, costly infrastructure, and the need for highly trained personnel. • Short intervals between screenings are required when used without HPV testing, indicating more tests needed that will lead to more visits and higher costs. • Specificity of cytology is decreased in countries with high HPV vaccination coverage due to the dramatic population reduction of high-grade lesions as a result of HPV vaccination
HPV testing	• Relies solely on the detection of HPV DNA, HPV mRNA or viral markers, not morphological interpretation. • Clinically validated HPV tests are more accurate and sensitive than primary cytology-based testing (e.g., conventional or liquid based Pap tests). • High clinical sensitivity. • High negative predictive value (NPV). • Low training requirements and a high throughput capacity. • Allows longer screening intervals than cytology-based screening leading to: less expensive programs and longer duration of "peace of mind" for women that test negative.	• High analytic sensitivity with potential increase in false positives causing more false referrals for colposcopy and biopsies. • Uncertainty caused by waiting for a diagnosis after a positive test may not be cost-effective if the prevalence of HPV infections is much higher than the prevalence of CIN (e.g., in young women). • More expensive than cytology alone. • Requires high-quality testing facilities. • If used without cytology, may increase referral to colposcopy given increased sensitivity causing more procedures and more costs. • If used with cytology as a triage tool, then clinicians must be willing to be more selective about which HPV positive patients to refer to colposcopy.
Co-testing	• Co-testing will result into earlier detection of abnormal findings before histopathologic diagnosis of cervical cancer made. • Leverage benefits of both tests to maximize sensitivity and specificity. • Allows institutions without FDA approved platforms for primary HPV testing to still do cervical cancer screening with HPV as co-test (not primary screening test)	• Costly. • Increases the number of tests performed. • Potentially increases referral to colposcopies. • Required validation if using off-label (non-FDA approved platform such as SurePath liquid based Paps with platforms that were FDA approved for ThinPrep). • Discrepant cases with only 1 test abnormal (HPV + /cyto- or cyto + /HPV-) and challenges on how to manage.

test in indeterminate cases with a diagnosis of atypical squamous cells of undetermined significance (ASCUS) on routine Pap test. It was not until 2014 that the FDA recognized HPV testing proposed in Roche's Athena trial as a primary cervical cancer screening method[4]. The same cervical sample used for liquid based cytology was found to be acceptable for HPV testing, however, instead of, or in addition to, placing the cervical sample on a microscope slide for morphological interpretation, the residual material in liquid preservative was found to be suitable for HPV testing. Recently, NGS (Next generation sequencing) assays have arisen that allow clinicians to check many genes of cancer simultaneously, and have been used along with PCR-based (Polymerase chain reaction) assays used to amplify a segment of DNA of interest. These methods allow the detection of the 14 h-HPV types, or HPV types 16/18 individually or together, in addition to mRNA detection methods to look at transcriptionally active HPV[4].

The main advantage of molecular HPV testing is its higher sensitivity in detecting severe dysplasia CIN2 + and CIN3 + , with more reliable detection of negative results. This was quantified via a European trial that showed a 30–40% gain in the sensitivity when HPV testing was used to detect CIN3 + , and higher negative predictive value. This unique trait of molecular HPV testing provides greater reassurance for women with negative results[18] and allows for a decreased need on highly trained pathologists to follow-up with additional morphological reviews. The higher sensitivity of the test also has the added advantage of increasing the screening interval (to 5 years), and providing a higher capacity for testing. HPV testing has also shown the ability to detect adenocarcinoma of the cervix, whereas cytology studies have shown that glandular lesions are notoriously a challenge on morphological reviews of Pap tests[18]. In summary, the longer interval that HPV screening allows between testing (5 years) in

comparison to cytology (3 years), makes molecular testing less costly of the two methods. The higher negative predictive value of HPV testing also provides an advantage in situations with low follow-up and affords a higher level of emotional and physical comfort for the women who test negative[1].

On the other hand, the low specificity of the HPV test has a large drawback in that it results in a large number of clinically insignificant positive results. This can lead to unnecessary referrals for confirmatory tests such as colposcopies and biopsies. In addition to the uncomfortable nature of the follow-up exams, the removal of cervical tissue can weaken the cervix, impact fertility, or lead to premature deliveries. These potentially unnecessary examinations can create excess psychological stress for a woman. Therefore, only HPV tests that have been proven to be highly sensitive for the detection of CIN2-CIN3 lesions should be ordered to reduce unnecessary diagnostic procedures[1].

The cost of HPV testing is entirely dependent on the availability of materials across different countries. So, in countries where cytology tests are less expensive than HPV tests, and there is a lack of infrastructure for high-complex molecular testing, HPV testing may not be feasible. Moreover, since the prevalence of HPV is higher in women less than 33 years of age, the high specificity of cytology screening might be favorable for these populations, resulting in a lower rate of unnecessary referrals and thereby increasing the cost effectiveness[1,19].

A new and emerging technique has been introduced known as CINTec plus cytology. This test is a qualitative immunocytochemical assay used as additional staining in abnormal cytology samples to simultaneously identify abnormal cervical cells with expression of p16 (a surrogate marker of HPV infection) and an elevated Ki67 proliferation. The CINtec PLUS assay has been shown to be more sensitive than cytology alone and more specific than HPV testing and could be used as an enhancement to diagnostic cytology if HPV testing results were positive, to determine if a follow-up colposcopy referral is required[20].

CO-TESTING

In 2003, the FDA approved co-testing (cytology and HPV testing together) as a part of the routine cervical screening for women ages 30 years old or older. However, it is important to remember that the FDA did not approve all of the HPV testing platforms with liquid based cytology methods (e.g., Aptima HPV testing was not approved with SurePath specimens); thus, in institutions using off-label methods, validation studies are needed prior to implementation. The 2012 ACS, ASCCP, and American Society for Clinical Pathology (ASCP) guidelines favored co-testing to be the primary method for women who are 30 years and older because of the increased reassurance of a double negative test (both cytology and HPV negative)[21]. Although HPV infections are more prevalent in younger sexually active women, the overall incidence rate of cervical cancer in these age groups is low. Therefore, the high sensitivity and decreased specificity of HPV testing in this age group will detect more HPV positive cases that have no carcinogenic abilities and result in unnecessary referral for colposcopy. Negative co-testing results in women 30 years old or older has been shown to be associated with a low risk of developing CIN 2 or CIN 3 in the following 5 years and can thereby safely provide reassurance to extend the screening interval to 5 years, opposed to 3 years with cytology alone[22,23].

Three large co-testing studies (Kaiser Permanente Northern California, Quest Diagnostics, and UPMC Magee-Womens Hospital) have shown that using co-testing will result in earlier detection of abnormal findings before histopathologic diagnosis of cervical cancer are made. Some studies have shown that 1 in 3 women who had CIN 2+ or 3+ could have been missed if HPV testing alone was done without the addition of cytology[24]. An article by Kaufman concluded that co-testing is more effective than cytology or HPV testing alone to detect invasive cervical cancer[21]. However, Kaufman's work was criticized in that the endpoint of cervical screening is to detect precancerous lesions such as (CIN2 + /CIN3 +) not invasive cervical cancer. Additionally, HPV testing has already proven to have a higher sensitivity than cytology screening tests, so including the cytology with HPV testing can have few benefits over utilizing the HPV test alone. Moreover, co-testing has been criticized for exposing patients to more tests, which could potentially increase the referrals to colposcopy, and raise overall costs and anxiety or discomfort for patients, while providing little reassurance in comparison to solely using the HPV test[25].

Using liquid based cytology with hr-HPV testing as a reflex test provides increased specificity for detection of high-grade lesions with high false positive rates. Since slightly over 50 percent of cytological test results show minor abnormalities[26,27], having hr-HPV testing as a reflex triage will decrease the referral rates to colposcopy and decrease the total abnormal cytology reporting rate. Another advantage of having reflex testing is to avoid the unnecessary psychological stress by decreasing the unnecessary referrals to colposcopies. HPV with cytology triage has the lowest sensitivity because the triage test negates the increased sensitivity of HPV testing. However, HPV testing with cytology triage may have the highest relative specificity. Between the two methods, studies have shown that the HPV with cytology triage required the least number of colposcopies to detect one CIN2 lesion or more severe lesion[28,29].

CONCLUSION

Over the past century, there have been major developments in cervical cancer screening, which have helped to provide improved, earlier detection of cervical cancer or its precursor lesions and improved the lives of so many women. With improvements and research into the biology of the disease, has come many different trials and perspectives on how to screen women. However, implementation of the perceived best screening method largely revolves around assessment of the resources available in a region, the practicality of implementation, and the risks deemed acceptable. In order to make these decisions, comparing the different methods, as done in this review, is important to make the optimal informed decision. While HPV tests are more reassuring when negative, in comparison to cytology alone, the lower specificity leads to more unnecessary referrals in the case of a positive test result and can increase patient anxiety. The Pap test, which has been improved over the years with liquid based cytology, has superior specificity but suffers in sensitivity compared to HPV testing. However, perhaps abandoning the Pap test, which has been successful for so many years, may not be prudent, as the Pap test has the added benefit of providing morphological review to increase the sensitivity of HPV testing and provide detection of non-HPV related infections and lesions. Creating initiatives to address the false negatives and lower sensitivity of Pap tests in some environments with high interobserver variability by centralizing Pap test interpretations to trained individuals with superior quality control or using new technology, may optimize this test instead of just abandoning it. Furthermore, providing physicians with guidelines (not mandates) that present options and allow them to decide as to the optimal screening method for their patient on a case-by-case basis may be ideal given the complexity of the issues at hand in different settings. This is particularly important for institutions that may not have an FDA-approved platform for primary HPV screening, and would allow those institutions to choose different screening options based on the resources available. In other environments, perhaps too many options introduce too much variability and is not practical for implementation, which would lead one to choose a different simplified cost-effective screening method, even if it

means sacrificing sensitivity or specificity. Ultimately, perhaps leveraging these two tests in a variety of different ways (e.g., co-testing, or HPV upfront with cytology triage, or cytology upfront with HPV triage) in different age groups may provide the optimal approach for cervical cancer screening, in regions where both tests are available. The data, as presented in this review, can be used to determine which is preferable given the age of the patient and the resources available. However, given the expansive variance in costs and resources available across different geographical regions, these comparisons are far from straight forward, and ultimately make it challenging to render definitive global recommendations.

In fact, there are a multitude of initiatives currently underway to assist clinicians, laboratorians, and patients alike to ultimately make the most informed decision regarding the proper screening methodology. The initiatives include continued evaluation by longstanding pathology society consortiums addressing the need to keep the guidelines fully updated, incorporating new technologies and data as needed. Some of these recent and ongoing efforts include:

1. The Cytopathology Education and Technology Consortium (CETC) represents a consortium of pathology societies involved with diagnostic cytopathology, and includes the American Society for Clinical Pathology (ASCP), American Society for Cytotechnology (ASCT), College of American Pathologists (CAP), Papanicolaou Society of Cytopathology (PSC), International Academy of Cytology (IAC) and American Society of Cytopathology (ASC), and has made strong efforts to comment on the most recent USPSTF and ACS screening guidelines and the ASCCP guidelines for management of abnormal cervical cancer screening tests. The issues raised included concerns over the lack of a co-testing option in the initial USPSTF guidelines and the issue of detection of cervical cancers that are HPV negative, in addition to stressing the importance of using an FDA-approved HPV testing method if performing primary screening. The advocacy by members of this group was instrumental in maintaining co-testing as a screening option[30].
2. The American Cancer Society (ACS) Sponsored Cervical Cancer Screening Initiative, with six workgroups focused on facilitating the transition to primary HPV testing, notably includes a Laboratory Infrastructure Workgroup, covering topics within the cytopathology laboratory to include quality assurance, testing platforms/equipment, and workflows. At the current time, the ACS upholds the use of routine cytology with HPV co-testing as the screening strategy most likely to diminish the adverse effects of either false negative cytology or false negative HPV screening test results. However, the choice of the optimal cervical screening method may vary for a variety of reasons, including patient and provider preference, in addition to geographic and socioeconomic considerations that may affect the choice of preferred screening in a specific country or practice setting[31].
3. The USPSTF has recently begun its next process (planned every 5–7 years) of data review, culminating with its updated recommendations for cervical cancer screening. Opportunities will be made available for public comment at major steps in its timeline, as seen with the recent open comment period for the draft research plan[32].
4. There is also an ongoing, formal Enduring Guidelines Effort for the 2019 ASCCP Risk-Based Management Consensus Guidelines to discuss, vet, and vote on new technologies, study new data, consider feedback from clinicians, which will allow assessment of ever-changing aspects of cervical cancer screening in order to decide how to modify the current guidelines in the future.
5. The renewed National Cervical Screening Program (NCSP) is an Australian initiative developed by the Australian Department of Health. In 2017, Australia was the first country to shift from a 2-year cytology testing to 5-year HPV testing with cytology triage. This incentive aims to provide universal access to cervical cancer screening by creating National Cancer Screening Register that actively invites women to participate in the NCSP, and the program even provides self-collection options to under-screened women[33]. Continual evaluation of the Australian experience will be critical to see the impact of primary HPV screening.

In the future, perhaps the cervical cancer screening story will have another chapter given the rapid development of technology, including enhanced imaging modalities, artificial intelligence, and molecular diagnosis, and its effect on science and the medical field. Advocacy efforts and increased evidence-based data will continue to be important to see which screening modalities or combination thereof will optimize cervical cancer screening in different settings.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary or referenced files/articles.

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M.S.: Conceptualization, literature search, data analysis, writing draft; S.M.: Conceptualization, supervision, editing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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