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Screening Tests and Support in Positive Human Papilloma Virus Tests

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Abstract

Screening for the detection of Cervical Cancer (CC) is moving from cytology or Papanicolaou (Pap) test to the detection of the primary high-risk Human Papillomavirus (HPV) test, based on evidence for this change, with support or triage options for positive HPV test results with better access innovations. The test of higher specificity such as cytology makes it an option for triage in positive HPV tests; but cytology and genotyping have been recommended for all positive HPV tests, especially for the other pool-positive hr-HPVs; but HPV-16/18 negative. Screening with primary HPV testing has been shown to be effective, affordable, and acceptable to women, especially in emerging countries; the use of Dual Staining (DS) to classify positive HPV results has higher sensitivity and specificity than HPV-16/18 genotyping or cytology at triage.

Conclusion: The transition to primary HPV testing instead of Pap testing for cervical cancer presents many challenges. The evidence supports it for its better sensitivity, and options for triage or HPV testing support are improving.

Keywords: Screening; Cytology; HPV tests and Triage; Colposcopy; Cervical cancer

Background

Cervical Cancer (CC) is a major global health problem with an estimated 604,127 new cases and 341,831 deaths in 2020 [1]. Almost 85% of the disease affects Low and Middle-Income Countries (LMIC), The World Health Organization (WHO) established the goal that all countries achieve and maintain an incidence rate of less than 4 per 100,000 women by 2030 as part of the Global Strategy to Accelerate the Elimination of CC. Although the traditional cytology or Papanicolaou (Pap) test has been the cornerstone of screening programs, its 50% sensitivity and limitations in accessibility require new strategies to achieve CC elimination. The discovery that infection with persistent oncogenic or high-risk human papillomavirus (HR-I-HPV) is an essential step in the development of CC that led to the development of HR-HPV-based diagnostic tests, which have higher sensitivity than cytology (96.1% vs 53.0%) but slightly lower specificity (90.7 vs 96.3%) for the detection of grade 2 or higher cervical intraepithelial neoplasia (CIN-2+) [2-6] Initially, the HPV test was incorporated as a method to classify Pap results with atypical squamous cells of undetermined significance (ASC-US), later the concept of joint tests or Co-testing (Pap plus HPV test) arose [2-5]. which have demonstrated efficacy of the primary detection of HPV [4-6]. In 2020, the WHO recommended HPV DNA tests as a primary detection method starting at age 30, with periodic tests every 5 to 10 years, for the general population [7]. Currently, the HPV-r test, primary It has been adopted in several countries, although there are currently 3 acceptable screening strategies: Pap, Co-testing and HR-HPV test, primary.

HPV Test

The American Cancer Society (ACS) specifically states that HPV testing alone is preferred every 5 years starting at age 25; Co-testing every 5 years or Pap alone every 3 years are acceptable [8]. The US Preventive Services Task Force (USPSTF) states that Pap alone every 3 years starting at age 21 and then HPV testing -ar, alone or Co-testing every 5 years or Pap every 3 years from the age of 30 are all acceptable strategies [9] (Figure 1). When applying these guidelines, it is important to keep in mind that they are intended for screening patients with all previous normal results without symptoms; This routine screening program for the detection of CC is not applicable in special populations, such as those with a history of abnormal results or treatment, immunosuppression [10], a history of HPV -related VIN or VaIN [11], or a history of hysterectomy for benign pathology without HSIL [12,13]. Rather, surveillance with interval testing in those who have an abnormal test result or prior treatment; its management is based on the risk provided by the American Society for Colpos copy and Cervical Pathology (ASCCP) [13,14]. Finally, the diagnosis is the evaluation (includes diagnostic Pap) in a patient with abnormal signs and/or symptoms (such as bleeding, pain, discharge or cervical mass) the evidence for the primary HPV test, the management of the options for a positive result it will improve the acceptance of the primary HPV test, as well as the accessibility to change the screening paradigm.

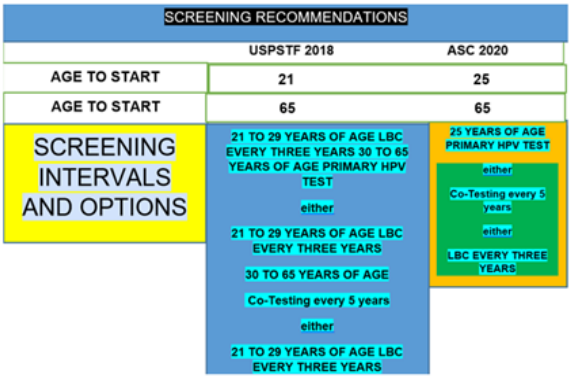

Figure 1: Recommendations on Screening for Cervical Cancer.

Evidence for Primary HPV Testing

HPV DNA tests are multiple that detect the DNA of hr-HPV genotypes, using multiple probes, for direct genomic detection or by amplification of the viral DNA fragment using the Polymerase Chain Reaction (PCR) [15,16]. Alternatively, tests based on HPV mRNA detect the expression of the E6 and E7 oncoproteins, viral integration markers [15]. Not all the tests used are approved by the (FDA) for primary HPV testing.

Approved HPV Tests

Currently, 2 tests are approved by the FDA for the primary detection of HPV. The Cobas HPV test (Roche Molecular Diagnostics) was the first approved in women 25 years and older 4, reports the combined results of 12 HPV-r (31/33/35/39/45/51/52/56/ 58/59/66/68) with reflex genotyping for HPV-16/18, offers the option of immediate triage for women with HPV+; it is also approved for Co-testing; the second approved BD Onclarity HPV test (Becton, Dickinson and Company) for the primary detection of HPV [17]; detects 14 HR-HPV genotypes, specifically HPV-16/18/45 Genotypes as well as HPV-31/33/35/39/51/52/56/58/59/66/68 Genotypes. Other HPV tests are approved for Co-testing and reflex testing, but not for primary HPV testing. The hybrid capture test (HC2) (Qiagen Inc) was the first approved HPV test in 1997 for reflex testing of women with ASC-US Pap. In 2003, it was approved for co-testing in women 30 years of age or older [15,16]. In 2009, the Cervista HPV HR test (Hologic Inc) was approved for Co-testing. The Aptima HPV test (Hologic Inc), also approved for Co-testing, is an RNA-based test that allows detection of E6/E7 mRNA with transcripts from 14 HPV genotypes [18].

Comparison of HPV tests with Pap

Data from 4 Randomized Controlled Studies (RCTs)-Swedescreen, POBASCAM, NTCC, ARTISTIC: with a total of 176,464 randomized participants screened with HPV or Pap test [19] Swedescreen and POBASCAM used GP5/GP6 PCR, while ARTISTIC and NTCC used HC2 for primary HPV test detection, the screening interval was 3 years in all but 5 years in POBASCAM. Pooled CC detection rate was similar, with a rate ratio for CC detection of 0.79 (95% Confidence Interval [CI], 0.46-1.36) in the first 2.5 years, but it was 0.45 (95% CI, 0.25-0.81), in favor of the HPV testing group, after 2.5 years. HPV testing was more effective in preventing cases of adenocarcinoma than Squamous Cell Carcinoma (SCC) (0.31 [95% CI, 0.14-0.69] vs. 0.78 [95% CI, 0.49-1.25]), HPV-based screening starting at age 30 provided 60 to 70% better protection than Pap. The result of the above meta-analysis was confirmed by the HPV FOCUS RCT investigating the efficacy of HPV testing (HC2) compared with Pap [20]. Detection rates for CIN-3 supported by primary HPV testing screening, with an absolute difference in incidence rate of 2.67/1000 (95% CI, 0.53-4.88) at study randomization and 3.22/1000 (95% CI, 5.12-1.48) at study completion 4 years later.

Co-testing and Pap: its benefit on the risk of CIN-3 based on HPV as Pap [21]; incidence rates of CIN-3 after 6 years of follow-up were consistently increased in HPV-positive women, and a positive result more accurately indicates CIN-3+ at 5 years than Pap alone. HPV negativity provided greater reassurance than Pap alone. At 5-year follow-up, CIN-3+ rates were 0.25% (0.12%-0.41%) for HPV-negative women compared with 0.83% (0.50%-1.13%) for Pap-negative women, With little difference in CIN-3+ rates between women with negative results on both tests and women who tested negative for HPV, the benefit of Co-testing is an important screening option. A study of 331,818 women enrolled for Co-testing at Kaiser Permanente found that the risk of CIN-3+ cited by HPV testing alone compared to Pap was significantly higher in both at 3 years (5.0 vs 3.8%; $p = 0.046$) and at 5 years (7.6 vs. 4.7%; $p = 0.001$) [22]. A negative Pap result did not reduce the risk of CIN-3+ for HPV-negative patients (3 years: 0.047 vs. 0.063%, $p = 0.6$; a 5 years: 0.16 vs. 0.17%, $p = 0.8$); a negative HPV test provides sufficient reassurance with low risk of CIN-3+ and an additional negative Pap does not provide additional reassurance, a systematic meta-analysis of 48 studies, including 8 RCTs, found that the addition of Pap to HPV testing increased sensitivity it is 2% for CIN-3 compared to HPV Test alone. This improves sensitivity at the expense of a considerable loss of specificity, with a ratio of 0.93 (95% CI, 0.92–0.95) for [23] CIN-3. The relative contribution of HPV and Pap testing in the detection of CIN was also evaluated. -3 and CC [24]. The HPV component alone identified a significantly higher proportion of HSIL and CC than Pap; 3.5% HSIL and 5.9% CaCu were preceded by HPV-positive results than Pap-negative results. Pap contributed only 5 cases per million women per year to co-testing sensitivity, but significantly more colposcopies, evidence suggests limited benefit from adding Pap to HPV testing [25].

Triage testing or support of a positive HPV result

The HPV test alone cannot discriminate between transient and persistent infections. Referral of all HPV-positive cases to colposcopy leads to overtreatment of associated unnecessary procedures, a triage strategy is essential to identify clinically important infections that truly require colposcopic evaluation; (Figure 2).

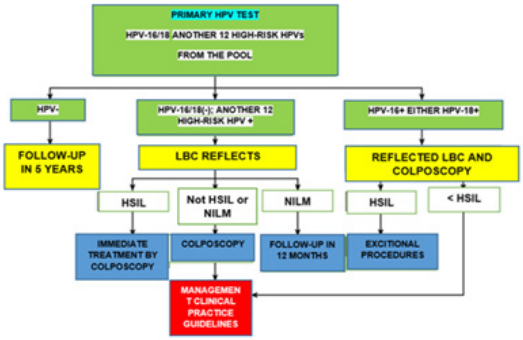

Figure 2: Management after detection with the primary HPV test for CC.

HPV genotyping

One strategy to classify a positive HPV test result is Genotyping. HPV-16 and 18 have the highest risk of persistence and progression and warrant immediate referral for colposcopy. On ATHENA, CIN-3 was identified in 17.8% (95% CI, 14.8-20.7%) of HPV-positive women [21-23], and Risk increased to 25.2% (95% CI, 21.7-28.7%) after 3 years. The 3-year risk of CIN-3 was 5.4% (95% CI, 4.5-6.3%) in women with HPV genotypes other than HPV-16/18. HPV-18 positive women had a 3-year risk that was intermediate between women with HPV-16 and women with the other 12 hr-HPV genotypes. Positive cases for HPV-16/18 are sent for immediate colposcopy and negative cases are followed up with Pap and colposcopy is only sent if Pap is ASC-US+ [26]. In July 2020, FDA-approved extended genotyping was performed with individual detection of HPV-31,51,52 (in addition to 16,18 and 45) and pooled detection of 33/58,35/39/68 and 56/ 59/66, individual HPV-16 and 31 genotypes carry baseline risk values for CIN-3+ (8.1% and 7.5%, respectively) that are above the 5-year risk threshold for referral to colposcopy based on risks of the ASCCP [27].

Pap or liquid-based cytology (LBC)

The greater specificity of the Pap makes it an option for triage of HPV-positive cases, and current management recommends triage for genotyping and Pap for HPV-positive patients, and especially if they are HPV-positive but HPV-16/18-negative. Pap results remain subjective than those of the primary HPV test, but the combination of the initial HPV test with reflex Pap is a reasonable and cost-effective option [13]. VASCAR found higher references to colposcopy in HPV in the screening group and cytology triage compared with Pap alone (19.36 vs. 14.54 per 1,000 women) [28] ATHENA investigated various triage strategies for HPV-positive cases and their impact of referral for colposcopy [4]. Use of HPV genotyping and reflective Pap, if HPV-16/18 was positive, colposcopy is sent, but if any of the other 12 HPV genotypes were positive, the reflective Pap was done If reported, they are re-evaluated with Co-testing after 1 year. Although this strategy reduced the number of colposcopies, referrals were higher in primary HPV testing (3,769 colposcopies per 294 cases) compared to Pap (1,934 colposcopies per 179 cases) or Co-testing (3,097 colposcopies per 240 cases) in 25 year old women [21-23].

p16/Ki-67 Double stain (DS)

Diffuse p16 immunohistochemical (IHC) staining, unlike focal staining, is associated with active HPV infection, can present in LSIL or HSIL [29] Ki-67 is a marker of cell proliferation. Coexpression of p16 and Ki-67 indicates a loss of cell cycle regulation and is a hallmark of neoplastic transformation. When positive, they are supportive of active HPV and HSIL infection. The addition of these stains to the Pap alone provides additional objective reassurance to the Pap, where inter- and intra-observer variability exists. These stains are performed using the FDA-cleared p16/Ki-67 Dual Stain (DS) single stains or IHC, CINtec PLUS Cytology (Roche Diagnostics), DS is not yet formally incorporated into triage algorithms, The IMPACT [30] evaluated the performance of SD compared to Pap in triage of HPV-positive results, with or without Genotyping of 20 HPV-16/18.35, of HPV-positive patients with DS results, the sensitivity of DS p16/ki67 for CIN-3+ it was 91.9% (95% CI, 86.1-95.4%) and 86.0% (95% CI, 77.5%-91.6%) in HPV-16/18–positive and in the other 12 genotypes, respectively. Using DS alone to classify HPV positive results showed significantly higher sensitivity and specificity than HPV-16/18 genotyping or Pap de triage for the other 12 genotypes, and higher sensitivity but lower specificity than using of Dad alone. DS p16/ki67 triage sent fewer women for colposcopy than HPV 16/18 genotyping or Pap triage for the other 12 genotypes (48.6 vs. 56.0%; $p < 0.0001$).

A retrospective ATHENA analysis of HPV-positive results in patients 25 years and older also demonstrated higher sensitivity of DS p16/ki67 compared with Pap (74.9 vs 51.9%; $p < 0.0001$) and similar specificities (74.1 vs 75%; $p = 0.3198$) 21-23 The PALMS, in women 18 years of age or older in 5 countries that was performed routinely with HPV, Pap, and DS tests, confirmed these findings [31]. The sensitivity of DS p16/ki67 it was greater than Pap (86.7 vs 68.5%; $p < 0.001$) for CIN-3+ with comparable specificities (95.2 vs 95.4%; $p = 0.15$).

Challenges and Opportunities

The historical success of the Pap in reducing the incidence of CC depended on the people who had access to the test. This continues to be true with the transition into screening with the primary HPV test. Limitations of HPV-based screening include physician and patient knowledge; access to evidence; cost; need for new laboratory infrastructure; need to take advantage of the electronic health record to record results, calculate patient risk, and determine next steps; and the need to re-educate patients and doctors about this new care model; medical groups are currently leading initiatives to help embrace primary HPV screening and to facilitate new approaches to care. The self-taking and independence of the subjective Pap would further improve access. Multiple studies of efficacy and patient acceptability have shown that primary HPV detection through self-sampling is effective, cost-effective, and acceptable for women, especially among less selected populations [32]. Sensitivity is comparable to samples obtained by the doctor with HPV tests based on polymerase chain reaction.

In addition, new molecular tests that detect target host genes with methylation. The viral genome can be used to classify HPV-positive cases. Several host methylation markers that identify host-specific genes (for example, CADM1, MAL, and miR-124-2) have been shown to be more specific, reproducible, and can be used in samples, as they are based on molecular methylation analysis [33] Incorporation of promising tests and approaches once validated and approved into risk-based management, and the risk calculator is also available [34].

Cost-Benefit

They are difficult to assess in the detection of CC, there are multiple factors and each country will have to design a CC detection, testing and treatment program that is appropriate in its context. The health economic model is based on PALMS and ATHENA; help to understand the cost-effectiveness of screening and support tests or triage for the detection of CC, the performance of the test and incidence of the disease determine if women are sent for follow-up tests or routine screening; on an annual basis, screening with primary HPV testing with triage or support with dual staining with p16 and Ki67 at ages 25-65 or 30-65 would mean health care savings; without being able to assess the anxiety it causes in patients [35-38].

Conclusion

The transition to primary HPV testing from Pap in the detection of CC presents many challenges, but also opportunities, the experience of countries that have already adopted the primary HPV test is crucial for the success and implementation of this new detection paradigm. The evidence supporting HPV detection at its best sensitivity is clear,

and existing triage options and innovations will continue to improve triage of patients with clinically important lesions as well as accessibility. With strong promotion and robust implementation, the WHO goal of eliminating CC and having 70% of women screened with a high-throughput test at age 35 and again at age 45 is achievable.

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The corresponding author takes full responsibility that all authors on this publication have met the following

required criteria of eligibility for authorship:

1) Significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data.

2) Drafting or revising the article for intellectual content.

3) Final approval of the published article.

4) Agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. Nobody who qualifies for authorship has been omitted from the list.

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