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REVIEW ARTICLE

Incorporation of HPV DNA Testing alongside Pap smears Increases Sensitivity for Cervical Cancer Screening

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ABSTRACT

Introduction: Cervical cancer is a malignant tumor that is caused by unremitting high-risk human papillomavirus (HPV) infection and is one of the most prevalent causes of cancer-related death in the world. Over the decades, major screening modality was cytology (Pap smear), but this screening modality is limited by low sensitivity. The review is a synthesis of peer-reviewed articles in recent few years to test the hypothesis that HPV DNA testing when used with cytology (co-testing), has a higher screening sensitivity and puts the proposed methodology into perspective of the newly developing paradigm of primary HPV testing. Consecutive evidence shows that a primary HPV test holds distinctly high CIN 2+ sensitivity (95.93) in comparison with the screening method (cytology 98.03), although with substantial better specificity (86.83) (moderately versus 79.83). Large-scale trials, however, have been able to establish significantly higher specificity (86.83), with a primary HPV test (95.93), which is comparable to secondary HPV testing.

Methodology: The literature search of the scientific literature published in the few past year was conducted systematically. The information was synthesised through randomised controlled trials, meta-analyses, epidemiological and clinical guidelines published by the leading organisations (WHO, ACS, ASCCP and FOGSI).

Conclusion: Cervical cancer screening has improved significantly in terms of sensitivity and long-term efficacy with the incorporation of HPV DNA testing. Although co-testing has been an important transitional model, it is now widely accepted that the new gold standard, primary HPV testing has provided an internalized position of clinical advantage (sensitivity) and possible harm (specificity, colposcopy rates). The eradication of cervical cancer globally has now become pegged on the implementation of these objective, high-performance molecular diagnostics through scalable, cost-effective and patient strategies.

KEYWORDS: *Cervical cancer, Human papillomavirus, Pap smear.*

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INTRODUCTION

The Changing Paradigm of Cervical Cancer Screening: The Papanicolaou (Pap) smear is a cytology-based assay that has been the backbone of cervical cancer prevention programs, supported worldwide and sustained over half a century, and is seen as one of the most important successful public health outcomes of the twentieth century that caused a drastic decrease in incidence and mortality. They were supported by these programmes, stating that cervical cancer is a preventable malignancy, which can be detected at an early pre-cancerous stage and treated.[1]

Dispite of such historical success, the cytological era is associated with limitations that have been well documented. The process is labor-consuming and thus requires a visionary infrastructure in the form of qualified cytotechnologists and pathologists to interpret the sample. More importantly, it has reduced clinical efficacy due to a significant sensitivity gap. Cytological sensitivity to detect cervical intraepithelial neoplasia grade 2 or more (CIN 2+) in a single round of screening is relatively low, ranging between 48.0% and 63.6%.[2] which means that a significant number of pre-cancerous lesions would be overlooked, requiring an increase of programmatic value through frequent and repeat screening (e.g., biennially).

The introduction of a high-risk (HR) HPV genotype as the essential etiology in more than 99% of cases changed the paradigm of cervical cancer screening by providing a molecular target upon which cervical cancer screening could be performed. Instead of using the morphological features of the disease, there could be a test to detect the causative

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agent, which will be the virus itself . This understanding has spurred the creation of HPV DNA testing and the concept of co-testing (cytology and HPV) whereby cytology and HPV testing are used side by side and is approved as an adjunctary screening measure in women aged 30-65.[2] This approach was seen as a way of maximizing the detection of HPV by combination of high level of test sensitivity (due to the detection of HPV) and a high level of specificity with familiar process of pap smear testing.[3-5]

The first assumption of this review, which is the evaluation of the so-called superiority of co-testing over cytology is a premise hypothesis which formed the initial paradigm change in screening strategy in the early 2010s. Nevertheless, over the years the scientific dialogue has grown through the volume of evidence created since 2013, and this question has become superfluous. Massive trials and meta-analysis have brought a more refined debate as to whether co-testing is actually better than or even necessary compared to primary HPV testing alone.[6] the review studies the significant programmatic, economic and implementation issues in this paradigm of molecular-testing, especially with the high-burden low-resource contexts like India, where 60% of cases are diagnosed at later stage.[7]

METHODOLOGY

A literature search of the scientific literature published in recent years was conducted systematically. The information was synthesised through randomised controlled trials, meta-analyses, epidemiological (GLOBOCAN and the National Cancer Registry Programme of India) and clinical guidelines published by the leading organisations (WHO, ACS, ASCCP and FOGSI). It has focused on comparative test efficacy, pathophysiology, impediments to implementation in the low- and middle-income countries (LMICs) and future technological advances.

Pathophysiology

Cervical carcinogenesis occurs via three stages (initiation, promotion, and progression).

The Etiologic Role of HR-HPV: Cervical cancer is a malignancy that has well-characterised etiologic agent. Aberrant persistent infection by a high-risk (HR -HPV)-genotype is the necessary but is not sufficient underlying cause of virtually all cases of cervical carcinoma.[3] Globally, HPV16 and 18 are the most oncogenic and most of these HPV infections are temporary and clear the host immune system within 1-2 years with no clinical outcome.

There are cofactors that license the probability of the infection developing into cancer in spite of the few infections that survive immune clearance to generate persistence. These are host immune status, where women with HIV are six times higher at risk of developing cervical cancer.[3] Other cofactors which have been documented are smoking, high parity and dysbiotic vaginal microbiome, which may have a local inflammatory milieu in favor of viral persistence and neoplastic transformation.

Molecular Processes

The E6 and E7 Oncoproteins: E6 and E7 oncoproteins are the primary causes of HPV-mediated oncogenesis in transient and productive HPV infection, E2 tightly regulates the expression of E6 and E7. Nevertheless, during a chronic evolving infection, the viral genome, frequently via sustenance of E2 gene is interrupted, leading to elimination of the E2-mediated suppression which causes the uncontrolled overexpression of E6 and E7 proteins.

Inactivation Tumor Suppressors: The over-expressed E6 and E7 proteins theatrically destroy the major tumor suppressor cascades of the host cell, and as such, take over with cellular apparatus to multiply the virus.

E6 Oncoprotein: E6 protein interacts with the p53 tumor suppressor protein. The p53 protein, known as the "*Guardian of the genome*" will stop the cell cycle and will cause apoptosis (programmed cell death) in case of DNA damage.

E7 Oncoprotein: The E7 protein is an antagonist of the retinoblastoma (Rb) tumor suppressor protein.[11] Rb protein is the standard cell cycle checkpoint that denotes the G1/S phase. E7 causes the degradation of Rb releasing the E2F transcription factor. E2F then indeed triggers the switch on of genes that stimulate the cell to hijack the checkpoint and go on an uncontrolled, unregulated proliferation spurt.

The Natural History of Disease

Infection to CIN: This molecular cascade directly translates into the clinical pathway of the disease and the disease pathology, which is as a rule a slow process in many years (18).

Infection: First infection of HR-HPV is obtained which is correspondingly in most cases during young adulthood .

Persistence & CIN: In a small group of the women, the infection is longstanding resulting in low grade cervical intraepithelial neoplasia (CIN1). This lesion is an indicator of productive infection by the virus and it tends to resolve on its own.

Progression (CIN2/3): The lesion can be driven to a high-grade CIN (CHIN2 and CIN3) through E6/E7 -driven genomic instability and uncontrolled proliferation, which is the actual pre-cancer state and the actual objective of all screening programmes.[10] The average time necessary to advance the lesion to CIN3 is 7-10 years.[18]

Invasive Cancer: When a CIN3 lesion is not detected and treated, it may go into the basement membrane to cause invasive cervical carcinoma.[8-20]

This is the pathophysiology behind the biological

justification of different screening modalities. Cytology (the Pap smear) is designed to identify the resultant morphological changes in cells (CIN), which occur late into the process. On the other hand, HPV DNA testing is sought to determine the etiologic agent the presence of HR-HPV DNA, which occurs years prior to the progression of high-grade disease. This time gap makes HPV more sensitive screening procedure that results in women who are at risk being identified before pre-cancer develops.

Health: Epidemiological Burden (Global and National Perspective)

Cervical Cancer in Third World Countries: Cervical cancer has been a critical issue facing the general public health and women in low-resource settings have been specifically affected by its severity and containment. World Health Organization (WHO) and GLOBOCAN (2022) note that cervical cancer is the fourth most commonly occurring cancer between women worldwide, with an estimated 660,000 women newly diagnosed with the disease in 2022 and nearly 350,000 women succumbed to the disease the year before. The most notable aspect in this global burden is that it is grossly unfair. A huge number of cases and deaths are surrounded by Low- and Middle-Income Countries (LMICs). The discrepancy in cervical cancer deaths that occurs in these countries is not due to any biological difference between these countries, but rather due to gross inequity in their access to the two main measures of preventive AIHPV vaccination to prevent cancer, as well as the secondary preventive measures of effective screening and treatment services.

Unless urgent actions are taken, the burden is estimated to grow as a result of population growth and aging, with predictions of 760,082 new cases and 411,035 deaths by the year.

The Indian Context: With India being a country with great geographic, social, and economic diversity, it has contributed much to the worldwide detrimental burden of cervical cancer, as data at the National Cancer Registry Programme (NCRP) has consistently revealed the cervix uteri as among the top five cancer locations in India, succeeding only by breast cancer. The cervical cancer epidemiology of India is very heterogeneous. The differences in the incidence at the population level as reported by population-based cancer registries (PBCRs) show significant spatial heterogeneity in the rate in terms of age-adjusted rates (AAR) per 100,000 women (23.3 in Mizoram and 6.4 in Manitoba), indicating challenges to effective prevention and control.

According to National Cancer Registry Programme (NCRP), the most critical measurement is the stage at which it is diagnosed, which has made the highest contribution to the high mortality rates in the country. The collective assessment of the hospital-based cancer registry (HBCRs) shows that 60.0% of patients with cervical-cancer in India arrive at their advanced-stages. This data is conclusive evidence of massive failure in the context of early detection. The early stages of cancer are commonly detected in the high-income countries (HICs) by means of screening, but in India pre-cancer lesions are often detected after the symptoms have taken effect, thus complicating the treatment procedure, increasing the costs significantly, and drastically reducing the chances of survival. Accordingly, high mortality rate of cervical cancers, the situation in India is not an oncological imperative, but it is indicative of failure or lack of screening programmes.

Risk Factors in India

Although high-risk human papillomavirus (HR-HPV) is the most common etiological cause of cervical cancer, case-control studies conducted in India have established a unique group of socio-economic and hygienic risk determinants that are closely linked to cervical cancer, which include:

- Low levels of education
- Rural residence
- Early age at marriage
- Lack of personal hygiene such as the use of old cloth sanitary napkins.
- Inaccessibility to or use of health services.[21-27]

All these factors are not biological risks in and of themselves but proxies of poverty, low health literacy, sex disparities, and systemic impediments to preventive care and thus need to be addressed with solutions that are both socially and logistically focused and medical ones as well.

COMPETITIVE EFFECTIVENESS OF PREVENTION STRATEGIES

Co-testing and Cytology (Validating the First Premise) *versus* Cytology Alone: The major theory that led to the abandonment of cytology was that the sensitivity could be improved by incorporation of HPV DNA test. This premise is overwhelmingly confirmed by the events of past few years and co-testing (concurrent HPV testing and cytology) has become the solution of choice over cytology in many HICs in women between 30 to 65 years of age.

This change was validated in a 2014 meta-analysis by Bouchard -Fortier *et al.*, of randomised controlled trials that found the relatively high sensitivity of co-testing at the baseline round (Risk Ratio 1.41 compared to cytology alone).

More to the point, detection rates at the second round of screening were also evaluated in the meta-analyses to find that co-testing product detects additional lesions, but also enables much earlier lesions of the pre-cancerous type to be eliminated and hence, allows the prevalence of the

high-grade disease among the population members to be reduced in the long term.

Co-testing vs. primary HPV testing: The Contemporary Discussion

The proved superiority of co-testing compared to cytology also led to the next scientific question- "*Does the cytology component really play an addition, or is the HPV tests that are high in number of sensitive enough?*" This controversy, which is between primary HPV testing and co-testing, has dominated cervical screening studies in the last ten years.

Sensitivity: Li *et al*. carried out a large 2022 randomised controlled trial in China that directly compared primary cytology, primary HPV, and co-testing to determine the prevalence of CIN2 + early cancer. Neither primary HPV nor co-testing showed statistically significant differences in sensitivity with cytology on its own.[3] Other clinical trials have also shown that the increment in sensitivity of cytology when combined with an HPV test is not significant.

Specificity and Harms: Specificity and harms are determining when comparative sensitivity occurs. In this case, the cytology paradox develops: the cytology element, though not having an effect on the sensitivity has appeared to reduce the overall specificity. Primary HPV testing 86.8 percent specificity, co-testing 79.8 percent specificity. Such a decrease in specificity causes an increase in the number of false positives, which exaggerates the number of unnecessary colposcopies and surgeries.

The Contradiction of Adenocarcinoma

There is a subtle controversy of identifying the adenocarcinoma (ADC) and the adenocarcinoma *in situ* (AIS). These lesions of the glands are notoriously hard to detect cytologically. The evidence from the majority of the data indicates that the endocervical canal is the location of these lesions and they most frequently are limited by cytology but diagnosed as having ADC due to their association with HR-HPV. However, there have been opposing results: a 2020 study found 100% sensitivity of Pap smears to AIS/ adenocarcinoma and 68.9% to high-risk HPV testing, and 30% of glandular lesions to be HPV-negative.

This worry has largely been quelled by long follow-up studies. A Swedish cohort study assessing long-term outcomes demonstrated no cases of cervical-cancer with a negative HPV but positive cytology outcome over the follow-up period and the benefit of the HPV reality test in all lesions would significantly outweigh the potential risk.[28-32]

Benefits, Harms and Limitations of Screening Modalities

Benefits: The most significant benefit of HPV DNA testing (whether as co-testing or as a primary screening) is the dramatically and non-negotiable increased sensitivity for high-grade pre-cancer (CIN2+ and CIN3+). This means that lesions will be detected at an earlier time to prevent them from becoming invasive cancer.

In an unbiased fashion, the most programmatic beneficial assessment stems from the highly sensitive (HPV testing) and thus, the extremely high Negative Predictive Value (NPV). If HPV testing is negative, this means a woman has a very low likelihood of developing cervical cancer anytime soon. This high NPV supports increased screening intervals from 3 years (cytology) to 5 years (HPV or co-testing) or even every 10 years under WHO guidelines. This means that instead of every 3 years, HPV/co-testing means every 5 years, which reduces the lifetime number of necessary screening tests, patient burden and programmatic costs over time.

The Cascade of Harm: This benefit of increased sensitivity comes at a high price for equitable limitations and generalized harm of decreased specificity. This is especially true for HPV testing that catches any and all strains of HPV, even the overwhelming majority, which are transient and clinically insignificant and merely spontaneously clear.

This means that low specificity, especially in younger populations, facilitates a cascade of harms:

Overdiagnosis: The test detects regressive lesions that will never become cancer, it's an overdiagnosis.

Increased Colposcopy Referrals: Higher cumulative percentage of positive HPV tests (not related to disease) corresponds to greater rates of colposcopy referrals

Patient Level Harms: The very act of screening and performing colposcopies is not without patient-level harm, including anxiety and psychosocial wellness concerns, complications, discomfort, pain, bleeding, and discharge.

Reproductive Harms: This is the most serious downstream adverse impact: iatrogenic. The excisional surgeries (e.g. LEEP) administered to remove the lesions observed (some of which can be over-diagnosed) have been linked to a predisposition of future adverse reproductive consequences, such as preterm birth.

This balance of benefits and harms has been quantified using modelling studies. In women having a high-sensitivity/ low-specificity test such as HPV, getting over-screened (e.g. annual), the cumulative cost of false positives and overtreatment may lead to negative net Quality-Adjusted Life Years (QALYs).

Laws (The Cost-Effectiveness Debate): With the trade-offs, the issue tends to focus on what is cost-effective. The literature on this subject in the past few years is very contradictory and context-specific.

Co-testing Support: According to some modelling studies, co-testing has more QALYs, is more effective at a cheaper cost than primary HPV testing.

Support of Primary HPV Testing: Other economic analyses on

the other hand reached a completely different conclusion. They discovered that primary HPV testing was more efficient and less costly than cytology and the extra price of adding cytology (i.e., co-testing) did not offer any significant clinical advantage but rather was not economically beneficial.

Context is Key: The absence of consensus implies that cost-effectiveness is not an absolute constant, but it is immensely subjected to local assumptions in the modelling, costs of the test, and the available infrastructure. An example of a study in Vietnam in 2025 established that cytology alone (5 times with intervals of 2 years) was more cost-effective than co-testing (3 times with 5-year intervals). This illustrates that what works best in HIC may not necessarily work best in an LMIC.[33-42]

Low-Resource Implementation Issues

Barriers to the Health System in LMICs: Implementation failure is the direct outcome of the epidemiological data that 94% of all cervical cancer deaths are seen in LMICs. The cytology-based programs that have proved successful in the HICs have not been effective in the low-resource environment. This is failed due to a plethora of barriers to the health system such as the absence of laboratory infrastructure, low quality control, inadequate information systems to follow-up and a serious lack of trained cytotechnologists and pathologists.

Although the HPV DNA test is more objective and does not depend on the subjective interpretation of morphologic results, it brings set of insurmountable challenges. In LMICs, including India pilot programs have faced major challenges:

Expense: The extreme capital expenditure of testing apparatus (e.g. PCR machines), proprietary samplers, and even the recurring cost of consumables are often above the budget limit of health ministries.

Infrastructure: The process of establishing an HPV testing lab is a logistical nightmare, in keeping with constant electricity access, cold storage of reagents, strong supply chains to deal with consumables, which is particularly challenging in remote or challenging locale.

Training and Linkage: Although the test is objective, the health providers still need immense training on how to triage the high population of the HPV-positive women and creating effective linkages with referral to treatment. A positive test and no avenue to treatment is a failed screening.

Patient-level Obstacles (Focus on India): Although screening services are available, its uptake is staggeringly low, even in most of the LMICs with most often less than 10%.54 This illustrates another, more profound group of patient and community-level barriers. A systematic review of HPV self-sampling implementation in India pointed out the major challenges related to the beneficiaries.

Knowledge and Fear: There is a large amount of misinformation and fear regarding the test, fear of the screening process and impressive fear of being diagnosed with cancer are the main reasons as to why women do not undergo the procedure.

Sociocultural Factors: Strongly embedded cultural stigma against gynecological exams and embarrassment coupled with social norms that insist on a husband to give permission or health needs of a woman, are strong obstacles.

Privacy: The absence of privacy was found to be a great impediment, especially among self-sampling in low-socioeconomic areas (homes with only one room and no indoor bathroom), the perceived loss of privacy to conduct the test is a major discouraging factor.

Effective Approaches to Barrier Overcoming

The barriers cause a sharp and deep gap between best and possible. The pragmatic resource-stratified strategy has already been developed as a result of primary HPV, which is cost-prohibitive and yet programmatically feasible. The old test (cytology) has already failed programmatically.

Pragmatism (VIA): In the context where HPV testing is not applicable, such strategies as Visual Inspection with Acetic Acid (VIA) are an important, low-cost option. Added to immediate treatment, VIA has proven to prevent more cancer deaths and is a foundation of LMIC screening initiatives.

Integration: The effective implementation will involve the engagement of state governments, as well as implementation of screening in already established and trusted health systems, including primary health clinics, HIV clinics, or maternal health services.

Self-Sampling: HPV self-sampling has become one of the most important ways to overcome health system barriers (it does not require a clinic visit and pelvic exam) as well patient-level barriers (it is less embarrassing and more private).[43-50]

GLOBAL SHIFT IN CLINICAL GUIDELINES

Clinical guidelines published in 2013 to 2025 period reflect the scientific community's response to the evidence presented in Section 5. These guidelines show a clear, global trajectory away from cytology and toward molecular testing, though the *pace* of this transition is heavily modified by local economics and legacy infrastructure.

World Health Organization (WHO): The guideline is a significant international shift, indicating a standard of science-first to be adopted worldwide by all nations. The guideline firmly supports HPV DNA testing as the optimal first-line screening methodology in all women. The guideline highly encourages the use of HPV tests in lieu of

cytology or VIA due to its high performance and low cost.

Key Recommendations

General Population: Screening should begin at age 30 years with an HPV DNA test with a 5-10 year screening interval.

Women Living with HIV: Screen it earlier (starting at age 25), screen it more often (at 3 to 5-year intervals).

This guideline forms the technical foundation of the WHO ambition of eliminating cervical cancer in the world 90% of the girls vaccinated by 15 years old, 70% of the women screened with a high-performance test by 35 and 45 years old and 90% of the women with pre-cancer or invasive disease receiving the right treatment.

United States (ASCCP/ACS/USPSTF): The guidelines 62 of the US represent in-between system, choked by a gigantic, established cytology infrastructure of its own.

The menu (USPSTF 2018): The US Preventive Services Task Force (USPSTF), whose recommendations are officially supported by the American Society for Colposcopy and Cervical Pathology (ASCCP) offers the three equally acceptable choices in women aged 30-65:

- Cytology alone every 3 years.
- HPV primary every 5 years.
- Co-testing every 5 years.

The American Cancer Society (ACS): guideline update was more prescriptive (The Preference): It also highly recommends primary HPV testing as the choice of testing, beginning at an earlier age of 25 and continuing to age 65. Co-testing is mentioned as being acceptable, but not preferred.

The explanation of this change, and why the menu still existed is instructive. The ACS and ASCCP admit that co-testing does not bring much more value to primary HPV testing; specifically, the question why all three options are not only still being maintained in US guidelines, but primary HPV testing is not being implemented in the US healthcare system at large because of the logistics of making the transition.

Indian Guidelines (FOGSI): Indian guidelines must be pragmatic and resource-stratified. The Federation of Obstetric and Gynaecological Societies of India (FOGSI) guidelines are a good illustration of such a strategy:

Good-Resource Setting: In areas with proper infrastructures, FOGSI suggests primary testing every 5-10 years, which is in line with the WHO.

Limited-resource Environment: In the environment where HPV testing is not possible, FOGSI suggests cytology after every 3 years or VIA after every 3-5 years.[51-57]

This guideline is specifically conscious of the implementation gap. It institutionalises the best vs. possible dilemma and offers a practical route of all the levels of healthcare as opposed to one impractical standard.

FUTURE OUTLOOK AND TECHNOLOGY IMPROVEMENT

The future of cervical screening lies not in the process of seeking a new test, but perfect implementation of the existing gold standard (HPV testing). The objective is a novel screening algorithm that will maximise uptake, sensitivity and specificity as a triad.

HPV Self-Sampler; *A Health Equity tool*: This is the most vital programmatic improvement, which is considered one of the major pillars of the WHO elimination strategy: uptake and access.

Influence on Uptake: Meta-analyses are conclusive. Providing women with an HPV self-sampling kit enhances the screening attendance (RR 1.9-2.1) in comparison to calling women to a clinic to collect a sample. It is effective especially in enhancing screening use among the under-screened and never-screened women who shun clinics because of financial, time, transportation, or shame factors.

Precision: Vaginal self-sampling was presented as clinician-collected samples, with similar accuracy, and identical sensitivity, with a reported validated high-performance PCR-based assay. Studies show vaginal sampling is more sensitive and accurate than urine-based self-sampling.

Sophisticated Risk Stratification (Solving the Specificity Problem)

The primary HPV testing has a major limitation it lacks specificity, causing the cascade of harms earlier discussed. The future of screening then, is more sophisticated triage tests to differentiate the women who are at risk and who have HPV (and require treatment) to those who are not at risk and who only have a transient infection.

P16/Ki-67 Dual Staining: This is a significant improvement of the test biomarker. It is not an HPV test, but an immunocytochemistry test that is a marker of concomitant overexpression of p16 and Ki-67. This only occurs in cases of cellular transformation by a virus (via E7/Rb) and not merely by the presence of the virus. Research indicates that it is more specific than cytology to triage HPV-positive women, to correctly determine who really has lesions of high grade and would need to undergo colposcopy.

HPV Genotyping: Kaplan: Not just a yes/no outcome, but the type of HR-HPV genotype. Women that are positive with HPV 16, 18, or 45 are at significantly greater risk of immediate cancer and can be referred directly to colposcopy, whereas women with other less aggressive forms of HR-HPV can be treated with more moderation.

The Post-Vaccination Era: The mass HPV vaccination is effectively decreasing the number of the most oncogenic

types of HPV and subsequently the rates of CIN. This health success presents a new statistical dilemma in screening.

The higher the decline in prevalence of true disease (CIN) in the population, the lower the Positive Predictive Value (PPV) of all screening tests. This implies that positive test is more apt to be false positive. The latter is most harmful to cytology, which already contains high levels of false positive outcomes. In a low-prevalence vaccinated population, an abnormal Pap smear will most certainly be a false positive triggering unnecessary intervention.

Digital Health, Artificial Intelligence (AI)

AI-based applications are becoming an urgent solution to the challenge of bridging the expert gap, especially in LMICs. AAI algorithms are being trained on automated reading of digital cytology images or colposcopy images. This will efficiently improve consistency and reduce expenditures in areas where there is not enough pathologists and gynaecologists (**58-73).**

DISCUSSION

This review attests that the thesis statement of the query by the user, namely that the sensitivity of incorporating HPV DNA testing with cytology (co-testing) is greater than cytology alone is supported unequivocally by the scientific literature of the past 12 years.[74] The synthesis of the scientific literature of the past 12 years exhibits that this thesis statement, however correct, has been replaced by the question in question. The information has pushed the discipline ahead and co-testing, the most developed strategy, has been seen as a transitional strategy.

This review finds the so-called co-testing paradox. The practice of HPV testing can be considered more efficient than co-testing in large-scale trials, including Li *et al*. (2022), which show that this practice leads to a cascade of harms, i.e. worse specificity, increased colposcopy referral rates, and reduced programmatic efficiency (more procedures per cancer detected) without statistically significant improvement in disease detection. However, it has to get along with contradictory literature. The first is the debate of cost-effectiveness, where some support co-testing,[40] and others support primary HPV.[41] This review attempts to reconcile this conflict by emphasizing the context-dependence of these models. The lesson of the Vietnam study is that cost-effectiveness in one area can be dissimilar in another.[42] The point is that cost-effectiveness is a local and not a global calculation and needs to be grounded on programmatic facts, rather than clinical efficacy.

The second contradiction is the question of adenocarcinoma. Although in one study,[31] a legitimate alarm was raised regarding the presence of HPV-negative glandular lesions, the follow-up data are very reassuring in the long-term[42] and other large-scale studies[29] are very reassuring that primary HPV testing is safe and effective in all types of cancer. This is nevertheless a sensitive field of post-market surveillance as nations switch over to primary screening of HPV.

The greatest discovery of this review is the tremendous implementation efficacy gap. The factual evidence points to a deadly lack of agreement between the best tests discovered during HIC clinical trials (primary HPV) and the potential test in a low-resource environment. The cost of the best test is reported to be beyond the budget capping, so it is no wonder that 60% of the cases in India are already at an advanced stage, nor that 94% of the deaths caused by cervical cancer are in the LMICs.[3,7] The cervical cancer issue is no longer a medical issue, but an implementation one.

This study is restricted to a review of already existing literature, but not a meta-analysis. The contradicting information on cost-effectiveness and adenocarcinoma, in its turn, will need additional, combined analysis to entirely clarify.

The future of cervical screening is a multi-step algorithm that will use the new technologies to address the following different challenges:

To the Unscreened: to break clinic, cost barrier, social barriers and reach the unscreened, HPV Self-Sampling.

In Sensitivity: Primary HPV Testing on that sample, to sensitively identify all the women who are at risk.[3]

To be Precise: Molecular Triage (e.g., p16/Ki-67 dual staining) to distinguish between transient infections and true, transforming pre-cancer and, therefore, avoiding the cascade of harms of overtreatment.[75,76]

This is the best, most efficient and fair route to go in the worldwide struggle against cervical cancer since this is an algorithm-based system.

CONCLUSION

History over the last ten years tells us all there is no doubt about the inclusion of HPV DNA testing in screening of cervical cancer, whether as co-testing or primary testing, it offers a better sensitivity and long-term protection against high-grade cervical disease than cytology itself.

However, the key conclusion of this review is that this technological change has already achieved its next stage. The rationale, as evidenced in massive trials and mirrored in worldwide guidelines, is overwhelming towards a clear abandonment of co-testing and in favor of primary HPV testing as the new gold standard. Primary HPV testing has a better balance between the programmatic advantages and harms, offering statistically equal sensitivity to co-testing and much better specificity, false positives and rates of invasive diagnostic tests.

The eradication of cervical cancer in the world, as it is

the goal of the WHO under its 90-70-90 strategy, is now technically achievable. Its implementation will depend not upon finding a new test, but upon resolving both the implementation and cost, as well as equity gaps, that must be overcome to make the best test available to the women who need it the most.

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