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Optimizing technology for cervical cancer screening in high-resource settings

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Abstract

Although historically successful in reducing the burden of cervical cancer, Papanicolaou (Pap) testing faces numerous limitations. A growing body of evidence suggests that modern screening practice will benefit from primary screening for high-risk human papillomavirus (HPV) infection, the causative agent of cervical cancer. Molecular tests detecting the presence of HPV nucleic acids consistently demonstrate high sensitivity relative to Pap testing, and provide reliable, dichotomous results. Pap cytology is ideally suited to triage HPV-positive cases owing to its high test specificity, and the accuracy of cytological readings will be maximized in high-prevalence conditions. This algorithm of primary HPV testing with Pap triage has been shown to maintain the high sensitivity of HPV testing without compromising Pap cytology's strong ability to rule out falsely positive diagnoses. Given the anticipated decline of high-risk HPV-16 and -18 infections in the emergent post-HPV vaccination era, highly sensitive primary HPV testing is especially warranted. Novel screening technologies that identify HPV viral gene expression continue to emerge and seek to complement current HPV testing by identifying those women who may be at risk of progressive disease. How to best incorporate these new technologies into clinical practice presents our next great challenge. Implementation of novel algorithms for cervical screening is not a trivial task. Avoidance of exceedingly complex screening algorithms is an important priority.

Keywords

cervical cancer; human papillomavirus; human papillomavirus vaccine; mass screening; Papanicolaou test; test performance

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Traditional screening practices

Screening efforts in high- and middle-income countries have been proven effective in reducing cervical cancer incidence and mortality. Driven by Papanicolaou (Pap)-based opportunistic and organized screening programs, roughly three-quarters of the disease burden has declined in the past 50 years [1]. This has made cervical cancer screening the most successful among prevention efforts for all malignant diseases. Trends in incidence and mortality, however, appear to have reached a plateau in recent years. Cervical cancer remains the second most common cancer in women worldwide and ranks seventh in incidence among women in developed countries [201]. The greatest burden occurs within developing countries, comprising just over 80% of globally reported cases [2]. Among those residing in developed countries such as the USA, the greatest burden of cervical cancer risk exists in under-served populations with reduced access to screening [3,4]. Regular participation in screening programs is an important concern that influences efficacy and disease outcomes, regardless of the screening tool used.

Pap cytology in its current primary screening role maintains several recognizable deficiencies. Most notable is the test's low sensitivity, estimated at 51% from a meta-analysis [5]. Sensitivity indicates the probability of a positive test result when the disease is present. Therefore, among women histologically positive for cervical lesions, Pap testing, at 51% sensitivity, will erroneously classify approximately half of the slides from women with lesions as negative. Avoiding the consequences from these false-negative results in clinical practice necessitates short screening intervals. For instance, cytology is performed at a minimum every 1–2 years commencing at age 21 in the USA [6], and in Canada, every year commencing at age 18 [7]. Not only is frequent testing inefficient in terms of cost, the high throughput of generally negative smears leads to cytotechnician loss of attention, fatigue and interpretation errors. Organized national screening programs, such as those employed in a number of European countries, alleviate some of the burden of screening frequency, enabling 3–5-year intervals between screening rounds [8]. Regardless of screening program, the reading of Pap cytology slides is highly subjective, necessitating rigorous quality control and quality-assurance practices [8]. Additional concerns include Pap cytology's poor ability to detect glandular lesions [9], and dependency on quality of samples, which may be obstructed by inflammation or cellular and noncellular debris.

Alternative technologies have been proposed to improve on conventional Pap cytology. One approach involves placing cell samples into a liquid fixative solution rather than onto glass slides. Automated liquid-based monolayer preparation, or liquid-based cytology (LBC; e.g., ThinPrep®, Hologic, MA, USA) is one example. Proposed advantages include reduced obstruction by extraneous materials and the possibility for ancillary molecular testing using the fluid. LBC has been widely adopted in clinical practice and policy makers in England and Wales have recently recommended and implemented LBC in their organized screening program [10]. Compared with conventional cytology, however, LBC has not been shown to significantly improve sensitivity, is more costly and is subject to many of the same interpretation issues [11].

Addressing deficiencies in traditional cervical screening has led to alternative screening paradigms such as those involving detection of the human papillomavirus (HPV). This article will discuss and build the case for molecular HPV testing in primary screening for cervical cancer, and will explore the many facets of modern practice in an era of multiple new screening and diagnostic technologies. For the purposes of this discussion, emphasis is placed on data and trials conducted in developed countries. There has been considerable progress in the evaluation of simple approaches to screening for cervical cancer in low-resource settings, in screen-and-treat situations such as the use of visual inspection with acetic acid. The interested reader is urged to consider excellent overviews on this topic [12–18].

HPV & cervical cancer screening

The causal relationship between HPV infection and cervical cancer has prompted inclusion of modern technologies into screening practices. Persistent high-risk (oncogenic) HPV infection is a necessary cause of precancerous and cancerous lesions of the uterine cervix [19]. Tests detecting HPV DNA are commercially available and have been approved for clinical use. The most widely used is the Hybrid Capture 2® test (hc2®, Qiagen, CA, USA), which detects the presence of 13 high-risk HPV (HR-HPV) types in cervical samples. The advantages of HPV DNA testing over conventional Pap cytology are many. Sensitivity of the test is very high, averaging 95% [20], ensuring a low frequency of false-negatives. The test is also objective, requiring no human interpretation, and performs as an automated procedure that requires minimal quality control and technician training in comparison with Pap cytology. A similar and more recently introduced test entitled the Cervista™ HPV HR test (Hologic) detects 14 HR-HPV types and has also been approved by the US FDA for clinical use.

In clinical practice, testing for HR-HPV DNA has largely been introduced as an adjunct to conventional cytology. Initial focus has been on triage to colposcopy, using HPV testing to guide management of women with mildly abnormal Pap cytology results. At present, the hc2 HPV DNA test has been widely implemented for triage of borderline Pap cytology results [21,22] (defined per the Bethesda classification as atypical squamous cells of undetermined significance [ASC-US] [23]). Driven mainly by a large body of evidence from the American National Cancer Institute's ASC-US/LSIL Triage Study (ALTS) for cervical cancer [24], triage with HPV DNA testing for ASC-US was shown to be as sensitive as immediate colposcopy and more efficient than repeat cytology [25–27]. Follow-up HPV DNA testing after excisional or ablative treatment for precancerous lesions, that is a 'test for cure', has also made inroads in clinical practice [26–30].

In the USA, a country in which concerns regarding malpractice litigation are particularly acute, dual-testing with both Pap and HPV DNA testing has also been recommended and implemented for women aged 30 years and older [31]. This approach makes the combined screening sensitivity exceptionally high, however, a premium is paid on overall specificity [20]. Specificity of a test denotes the probability of a negative test result when the disease is not present. Dual-testing therefore increases the frequency of referrals for colposcopy and false-positive diagnoses, and the consequences of this will be discussed later. Furthermore,

combining two tests has shown only a marginal benefit in detecting high-grade lesions in comparison with HPV DNA testing alone [32]. Of greatest concern, however, is that dual-testing is impractical for most healthcare systems, requiring a doubling of tests, and is therefore extremely costly.

Although screening strategies such as cytology with HPV triage and dual-testing serve to improve existing screening practices to a certain extent, both methods arguably fail to resolve the aforementioned issues with Pap cytology. It is becoming increasingly important to consider alternative paradigms in which less focus is placed on cytology as the primary screening test.

Current screening in the era of prophylactic HPV vaccination

Modern cervical cancer control embraces the unique ability to combine primary and secondary prevention efforts. Primary prevention from targeted HPV infections has been made possible through prophylactic HPV vaccination. Two commercially approved vaccines, including quadrivalent Gardasil™ (Merck) and bivalent Cervarix™ (GlaxoSmithKline, Uxbridge, UK), immunize against HR-HPV genotypes that are responsible for 70% of all cervical cancers, namely HPV-16 and -18 [33,34]. Vaccinated women without prior infection will be fully protected from developing HPV-16 and -18 infections over many years. Women with previous exposure may not be protected or will benefit to a much lesser degree, and prevalent infections are not treated by the prophylactic vaccines. However, early evidence from Phase III vaccine trials indicate partial cross-type protection against HPV-16-related oncogenic types 31, 33, 52 and 58; and HPV-18-related oncogenic type 45 [35,36]. Furthermore, female vaccination is also expected to have a moderate indirect effect on the rates of HPV infection and related diseases through herd immunity [37]. The projected clinical impact of prophylactic HPV vaccines estimates a reduction of up to 51% of total invasive cervical cancers [38].

Forecasting shifts in incidence and prevalence of HR-HPV infection postvaccination is a process filled with complexity. The most important public health dividend from the changing epidemiology of HPV infection postvaccination will be the gradual decrease in prevalence of cervical disease, which will directly influence the positive predictive value (PPV) of a diagnostic test. Simply described, a test's PPV indicates the probability that a woman who tests positive actually has the disease. The PPV decreases with reductions in prevalence, meaning increasingly more women in the postvaccine era will receive false-positive diagnoses, causing excess medical intervention and worry. The sharp decline in PPV across several lesion prevalence rates is illustrated in Figure 1, assuming constant Pap test sensitivity and specificity (51 and 98%, respectively [5]) [39]. As shown, there will be a sharp decline in the PPV of Pap cytology as lesion prevalence falls to less than half of today's typical caseloads of 10%, seen in many high-risk areas.

Ordinarily, while positive and negative predictive values are directly influenced by lesion prevalence, sensitivity and specificity estimates remain constant and intrinsic to a test. However, Pap test sensitivity and specificity may deteriorate on account of the subjective nature of conventional cytology in the postvaccine era [39,40]. For instance, with decreased

lesion prevalence, sensitivity may decline as a result of reduced attention paid to slides that are generally unremarkable. This will lead to even more false-negative diagnoses, rendering the test virtually ineffective. Potentially compounding the problem, specificity may decline as cytotechnologists, under heightened awareness of potential false-negatives, assign greater importance to what would otherwise be a negative smear. False-positive results would arise as a consequence, contributing to excess colposcopy referrals and patient stress.

These potential qualitative changes in Pap cytology due to reading performance emphasize the need for heightened attention to quality control and assurance practices in the postvaccine era. Avoidance of test inaccuracy and wasted resources is achievable by improving the existing screening paradigm that focuses on conventional Pap cytology [41]. Greater attention needs to be paid to molecular HPV testing, which is not subject to the same inconsistencies, particularly given the forthcoming decline in prevalence of HPV infection.

Modern screening opportunities

Discontinuing screening in the postvaccine era is not a viable option. Current vaccines do not protect against all HR-HPV types, and questions remain unanswered regarding the duration of protection, and the long-term efficacy of cross-protection from other HPV genotypes [42–44]. In addition, patient uptake and adherence to vaccine schedules will each play critical roles. As evidence in favor of primary screening using HPV DNA testing grows, the modern cervical cancer screening paradigm continues to evolve. The superior sensitivity of HPV DNA testing compared with conventional cytology is now well established. As mentioned previously, HPV DNA testing offers nearly doubled sensitivity (95%) in the detection of high-grade cervical lesions or cancer compared with conventional cytology (51%). Pooled relative sensitivity and specificity estimates (HPV DNA test: cytology) from a number of randomized and nonrandomized studies from the past decade were meta-analyzed by Cuzick *et al.* [20], demonstrating a 14% higher sensitivity of HPV DNA testing compared with cytology. More recent randomized controlled trials (RCTs) designed to evaluate primary HPV screening offer further support to these findings [45–49]. Figure 2 displays relative sensitivity and specificity estimates from a number of recent randomized and nonrandomized studies. Existing overviews of screening RCTs and their findings are available [50,51], and a large-scale meta-analysis of HPV in the role of primary screening by the *Cochrane* collaboration is currently underway [202].

The prevailing concern with implementation of HPV DNA testing is the lower specificity in comparison with conventional Pap cytology. On average, studies have demonstrated specificity of HPV testing to be between 5 and 10% lower than conventional screening [52–54]. Under more controlled conditions, however, a screening RCT from North America, the Canadian Cervical Cancer Screening Trial (CCCaST), found HPV test specificity to be 94.1% compared with Pap cytology at 96.8% [46]. Lower specificity translates to increased false-positive diagnoses, potentially resulting in unnecessary colposcopy referrals. In clinical practice, a test's specificity is also a main driver of cost, which underscores the perception that HPV DNA test specificity requires improvement.

The relationship between age and persistence of HPV infection is another important factor warranting consideration. Sensitivity of HPV DNA testing is highest in younger women (i.e., under 30 years of age) in whom infections and minor lesions are common but also highly transient [53]. Identification of HR-HPV in a young woman, therefore, does not necessarily indicate the likelihood of progression to a high-grade lesion or invasive disease. Treatment of regressive low-grade cervical lesions may also be potentially harmful to women in this age group as complications associated with postexcisional treatment include perinatal mortality and adverse pregnancy outcomes [55].

While screening tests may have individual performance limitations, it is possible to account for them concurrently. A strategic combination of screening technologies will enable maximization of test properties while maintaining existing infrastructure and potentially saving costs.

Optimizing screening in the HPV vaccine era

In the post-vaccine era, screening would arguably benefit most from an algorithm that utilizes primary HPV DNA testing followed by Pap cytology for triage. From a theoretical perspective, this algorithm maximizes test properties, capitalizing on the high sensitivity of HPV testing and the high specificity of cytology [39,40,56,57]. According to this sequence, Pap cytology is reserved for triage of women who test positive for the presence of high-risk HPV genotypes. Serial testing in this fashion is commonly observed in other disciplines of medicine (e.g., syphilis screening). Evidence in support of HPV DNA screening with Pap triage continues to grow, demonstrating improvement in both test accuracy and cost-effectiveness. A screening RCT employing this algorithm within the Finnish Organized Screening Program identified marked improvements in the detection of cervical pre-cancers overall [45], and demonstrated higher specificity than conventional screening in women aged 35 years and above [58]. Data from the Italian New Technologies for Cervical Screening (NTCC) RCT similarly support these findings, encouraging the use of Pap cytology to direct referral to colposcopy in HR-HPV-positive women aged 35 years and older [49]. In Western Canada, RCT of HPV testing for cervical cancer screening (HPV-FOCAL trial) is currently underway, and also aims to establish the efficacy of HPV testing with cytology triage via LBC [59]. Recent studies of cost-effectiveness further support this novel algorithm, showing reductions in cost when compared with conventional Pap-based screening in North American [60–62] and European [63] settings.

One of the most important advantages of primary HPV DNA testing is that negative HPV test results afford greater reassurance of the absence of cervical lesions. This enables extended intervals between screening rounds for up to twice the maximum duration permitted by conventional cytology [64]. A recent study reported significantly lower breakthrough rates of high-grade lesions from HPV DNA testing at 6-year intervals compared with cytology at 3-year intervals, concluding that screening half as often with HPV DNA testing gives twice the protection of conventional cytology [32]. Evidence from subsequent screening rounds from multiple randomized trials provide additional support in favor of lengthening screening intervals between HPV DNA tests [47–49]. It is recognized

that screening intervals may extend upwards of 5–6 years or potentially up to 10 years. This question is expected to be answered upon completion of follow-up in screening trials that are currently underway [46–49,65–67].

Primary HPV screening will also ensure that many of the qualitative concerns regarding subjectivity of conventional cytology screening are resolved. In the post-vaccination era, the benefit of cytologic triage will be especially crucial owing to the rarity of HR-HPV infection. When cytology is placed in the context of a triage test, the cytotechnologist's case load will decrease, but will represent a more rewarding experience in reading smears because lesion prevalence will be higher, enabling maximization of the PPV and overall clinical utility [5,39,68]. The cytology case load will therefore be 'artificially enriched', enabling cytotechnologists to assess slides from HPV-positive women only.

Emerging molecular markers

Technologies enabling early detection and prevention of HPV infection are continuing to emerge and advance. While current clinical HPV DNA tests (e.g., hc2) inform presence or absence of infection, emerging technologies aim to detect transformation and dysplastic lesions. Promising technologies with the potential for clinical application may be divided into three broad categories: DNA-based, mRNA-based and protein-based tests. First, DNA-based genotyping tests discriminate between certain HR-HPV genotypes, thus improving the specificity of standard presence/absence-based HPV DNA tests, such as the hc2. For instance, assays detect high-risk genotypes (e.g., HPV-16), which are associated with a greater absolute risk of high-grade cervical lesions [69]. DNA-based genotyping for HPV-16 or -18 infections could therefore help inform the necessity for repeat testing or further investigation. Second, mRNA-based tests detect persistent expression of viral oncogenes *E6* and *E7*, a necessary step for HPV-induced carcinogenesis. The detection of viral mRNA transcripts with assays such as the APTIMA® (Gen-Probe), PreTect HPV-Proofer (NorChip, Oslo, Norway) or NucliSENS EasyQ® HPV (bio-Mérieux, Marcy l'Etoile, France) may more efficiently delineate clinically significant infection in comparison with HPV DNA detection assays [70]. Preliminary demonstrations have shown that the presence of E6/E7 mRNA transcripts in HPV DNA-positive women is more strongly associated with persistence of infection in a subsequent screening round when compared with women only positive for DNA at baseline [71]. The ability to discriminate persistent from transient infections is of particular interest, particularly if primary molecular screening is to be applied to women under 30 years of age. The mRNA HPV assay APTIMA, for instance, has recently shown promise as a routine screening option within a population-based setting in France [72]. Third, an emerging protein-based test enables detection of the protein p16INK4a (p16; e.g., CINtec®PLUS, mtm laboratories, Heidelberg, Germany), which marks cells activated with viral E6/E7 oncogene expression. Evidence at this time suggests a positive association between p16 and high-grade cytological and histological abnormalities, although reproducibility and interpretation of the test are said to require improvement [73]. p16 has been demonstrated to be a sensitive biomarker in screening for high-grade cervical neoplasia, with high specificity and negative predictive value compared with HPV DNA testing [74,75]. Numerous investigators have now assessed the utility of p16 as a triage test for ASC-US and LSIL cytology [76–83], and in triaging patients testing positive for HPV

[84]. Generally, these studies support the application of triage by p16 immunostaining in women with equivocal results from cytology, as well as those who are HPV-positive. In the postvaccination era, biomarkers such as p16 may eventually play an important role in screening and reducing diagnostic variability of cervical biopsies [85].

Before these new technologies may be adapted for clinical practice, accumulation of more clinical data is essential. With the exception of one very large clinical study [86], most assessments have been limited to academic laboratories and based on small samples. In order to inform existing practice, emerging and ongoing clinical studies must compare novel screening test results with existing validated HPV DNA tests. The bottom line for clinical relevancy is that assays must be accurate, of minimal cost and easy to perform. More detailed summaries of emerging molecular tests have been made by Wentzensen *et al.* [87] and Szarewski *et al.* [88].

Integrating future technologies

As screening technologies for cervical cancer evolve, consensus clinical management algorithms must evolve concurrently. At present, algorithms in cervical cancer management are made on the basis of combining cytological, molecular, colposcopic and histological information from patient histories. As new technologies emerge and are added to the equation, a multitude of possible combinations of test results will arise, resulting in exceedingly complex decision trees. It is easy to imagine management scenarios of ambiguous nature that will arise, especially under the novel paradigm of primary screening with molecular HPV testing.

Integration of the screening sequence of HPV DNA with Pap triage will not be without certain difficulties. Generating substantial discussion is the scenario of HPV-positive and cytology-negative cases. Current recommendations in the USA are to follow-up with dual testing after 1 year rather than immediate referral to colposcopy [47,48,89,90]. Notably, follow-up rates of these women, particularly those with lower grade lesions, will ideally be high in order to maximize the benefit of HPV testing [67,91]. Already, however, new candidate technologies are being proposed to fill the triage role. The American Society for Colposcopy and Cervical Pathology (ASCCP) has approved DNA genotyping tests for HPV-16 and -18 (e.g., Cervista HPV-16/18) in the USA to test women aged 30 years or older who are HR-HPV-positive and cytology-negative [90]. As mentioned previously, p16 testing is a tool that may alternatively emerge for diagnostic triage [73].

Aside from the complications arising in the algorithmic approach from various emerging screening tests are the characteristics of women themselves. Age remains a major predictor of cervical disease progression. In younger women (i.e., under 30 years), avoidance of false-positive test results is of particular importance, and separate guidelines based on age may be implemented. At present, Pap cytology remains the only approach for screening women younger than 30 years of age although there is still a possibility that Pap triage using HPV DNA as the primary screen may work for women as young as 25 years of age. Long-term results from screening trials are pending, and will inform strategies to screen younger women. Moreover, in the postvaccination era, the discrepancy between vaccinated and

unvaccinated women will add another important dimension to the complexity of screening algorithms.

Accounting for the countless screening and diagnostic test combinations with patient-specific characteristics will undoubtedly generate much confusion for both policy makers and clinician decision making. Avoidance of complex, convoluted screening algorithms as new technologies emerge should be a priority. Improper usage of novel screening and diagnostic tests as they emerge may actually increase screening costs or result in patient harm. To guide the prevention of cervical cancer and better amalgamate patient information, Castle and colleagues have proposed a cervical cancer prevention system based on risk assessment [92]. The course of management will be based on defining a patient's risk stratum, defined by age and vaccination status, in addition to all available molecular, cytologic, colposcopic and histological information. At present, the tool is under development, and will likewise build on data from clinical trials and longitudinal studies currently underway.

Expert commentary

Human papillomavirus vaccination is expected to reduce the burden of cervical cancer in most settings; however, since it does not protect against all oncogenic HPV types and not all women at risk for cervical cancer are being targeted for vaccination, future cervical cancer prevention campaigns will have to include screening. Despite the many advantages to primary screening using HPV DNA testing and triaging HPV-positive cases using cytology or other technologies, many countries and jurisdictions are still uncertain on whether it is safe to abandon cytology as the primary screening tool. This means that for the time being cervical cancer screening will not change much in most settings; that is, most government and managed care organizations will continue to support a primary screening approach that includes cytology, either as a standalone test or with adjunctive HPV testing.

In addition to the scientific reasons for eventually dropping cytology from primary screening, sustaining this uncertainty will likely become too costly when considering the substantial added cost of vaccines to prevention campaigns. We must not be naive in believing that science alone will lead to a change in policy. Ultimately, policy makers will likely be swayed by results from demonstration projects suggesting favorable cost-effectiveness resulting from the fact that HPV testing may eventually become more affordable than cytology owing to:

- High volume testing if adopted as the primary test;
- Safely extending screening intervals under the HPV/Pap triage screening paradigm, (e.g., from 1–3 years to 3–5 years for women who test negative on both tests), which will lead to fewer tests overall.

However, important questions must be answered before implementing HPV testing as a population screening tool, such as:

- What will be the role of HPV typing and other markers of disease progression?
- What is the optimal age to initiate screening?

- What is the appropriate follow-up algorithm for women who test HPV positive and Pap negative?

From a clinical perspective it is imperative that screening algorithms are not complicated, otherwise it may be unrealistic to expect clinicians to accurately incorporate these new technologies.

Five-year view

Owing to the latency in progression from high-grade lesions to invasive cervical cancer, a delay of 10–15 years post-HPV vaccination implementation may be expected prior to an observable reduction in incidence. This will depend largely on HPV vaccine uptake in the immediate future and the time it will take vaccinated women to reach screening age [39]. It is essential in the short term, therefore, to plan surveillance mechanisms that can integrate the information from cervical cancer screening and HPV vaccination. Record linkage between vaccination registries and HPV screening databases will enable assessment of the duration of protection afforded by vaccination, and assess any disparities between vaccinated and unvaccinated women [93]. Countries with publicly funded vaccine catch-up programs (e.g., Australia [94]) will expect to observe the effects of vaccination sooner, hastening the need to put surveillance procedures into place.

A persistent message throughout this discussion is that there is much to be revealed in the next several years from ongoing cervical cancer screening trials. Priorities include ascertainment of the duration of protection offered by HPV vaccines, and establishing the evidence base to support implementing primary screening with molecular HPV testing. As trial follow-up continues, the growing body of evidence will reveal suitable screening intervals, and inform healthcare professionals of emerging risk assessment and referral strategies. Owing to the maturing understanding of the biology behind cervical cancer progression, novel molecular biomarkers will also reach sophistication and find their place in clinical practice. Incorporating an innovative risk-assessment strategy as proposed by Castle [92,95] shall prove to be flexible to the growth of these new technologies.

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Key issues

- Conventional Papanicolaou (Pap) cytology is limited as a primary screening tool, despite advances in technology such as liquid-based cytology.
- Human papillomavirus (HPV) DNA testing is highly sensitive and objective, which makes it an ideal replacement for Pap cytology in the role of primary screening.
- Conventional Pap cytology has high specificity, making it an ideal triage test subsequent to primary HPV DNA testing.
- Prevalence of cervical lesions will decline in the era post-HPV vaccination, emphasizing the need for highly sensitive HPV DNA tests in the primary screening role.
- Advances in molecular testing will enable more insight into the likelihood of infection persistence and have the potential for triage of HPV-positive individuals.
- Incorporating novel screening and diagnostic tests into clinical practice will require careful strategic planning to avoid potential patient harm and increased screening costs.
- Novel strategies based on risk assessment may show promise in defining the appropriate courses of management through each patient's screening trajectory.

Figure 1. Influence of lesion prevalence variation on the positive predictive value (red curve) and negative predictive value (blue curve) for Papanicolaou cytology

Different lesion prevalence rates (0.5, 1, 5, 10, 20 and 50%) are shown as dots in the curves. The green inset 2×2 table shows an example of results in a hypothetical sample of 1000 women with 10% lesion prevalence. The corresponding PPV and NPVs are 73.9 and 94.7%, respectively. The purple inset table illustrates the situation when lesion prevalence is 1% (10,000 women in the sample). The corresponding PPV and NPVs are 20.5 and 99.5%, respectively.

Assumptions: constant 51% sensitivity and 98% specificity. The formulas used for PPV and NPV are: $PPV = \text{Sens} \times \text{Prev} / [\text{Sens} \times \text{Prev} + (1 - \text{Spec}) \times (1 - \text{Prev})]$ and $NPV = \text{Spec} \times (1 - \text{Prev}) / [(1 - \text{Sens}) \times \text{Prev} + \text{Spec} \times (1 - \text{Prev})]$.

NPV: Negative-predictive value; PPV: Positive-predictive value; Prev: Prevalence; Spec: Specificity.

Modified from [39].

Figure 2. Relative (A) sensitivity and (B) specificity of HPV DNA testing compared with cytology to detect cervical intraepithelial neoplasia grade 2 or worse in primary screening studies

(A) Ages 25–34 years; (B) Ages 35–60 years.

†Randomized clinical trial.

CI: Confidence interval; HPV: Human papillomavirus.

Original data source: [20].

Data taken from [46,58,67,89,96–111].