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INTEGRATION OF HPV SELF-SAMPLING AND AI-ENHANCED CYTOLOGY IN CERVICAL CANCER SCREENING PROGRAMS

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Annotation: Cervical cancer remains a major cause of morbidity and mortality among women globally, despite being one of the most preventable malignancies. In 2020 alone, an estimated 604,000 new cases and 342,000 deaths were recorded worldwide, with the highest incidence occurring in low- and middle-income countries where access to screening and early treatment is limited. Screening programs based on conventional cytology (Pap testing) have significantly reduced cervical cancer incidence in high-income settings. However, in resource-constrained environments, gaps in accessibility, infrastructure, and follow-up systems have hindered the establishment of effective screening coverage.

In the last decade, two major innovations have transformed cervical cancer prevention: (1) high-risk human papillomavirus (HPV) testing using self-collected samples, and (2) artificial intelligence enhanced digital cytology for accurate and scalable triage of HPV-positive cases. HPV self-sampling allows women to collect vaginal specimens privately and conveniently without requiring a pelvic examination, resulting in dramatically improved participation rates, especially among under-screened or never-screened women. Meanwhile, artificial intelligence (AI) applied to digital cytology has shown diagnostic sensitivities and specificities comparable to expert cytopathologists, while reducing inter-observer variability, workload, and false-negative rates.

This article synthesizes the global evidence on integrating HPV self-sampling and AI-enhanced cytology into national cervical cancer screening programs. It reviews diagnostic performance metrics, implementation strategies, infrastructure requirements, population acceptability, clinical workflow models, cost-effectiveness, and challenges unique to diverse health systems. Drawing from multicountry trials and implementation studies, the article proposes a model for large-scale adoption of integrated HPV self-sampling and AI cytology pathways, highlighting opportunities to accelerate progress toward the World Health Organization's cervical cancer elimination targets.

Keywords: Human papillomavirus; HPV; self-sampling; cervical cancer; AI cytology; digital pathology; deep learning; screening programs; LMIC; CIN2+; cervical precancer; triage algorithms.

Introduction. Cervical cancer is the fourth most frequently diagnosed cancer among women globally. Over 90% of cervical cancer deaths occur in low- and middle-income countries

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where organized screening systems are inadequate or absent. The disease is caused by persistent infection with high-risk HPV genotypes, most commonly HPV-16 and HPV-18. Although HPV vaccination provides primary prevention, global disparities in vaccine availability mean that screening will remain essential for at least the next 50 years.

Historically, cytology-based screening (Pap tests) has been the foundation of cervical cancer prevention. While highly successful in high-income countries, its effectiveness depends on robust laboratory systems, consistent quality assurance, and regular screening intervals—conditions often lacking in many regions of the world. Additionally, cytology's sensitivity varies widely, with reported ranges of 50–70%, leading to missed cases.
HPV testing has emerged as a more sensitive primary screening method, detecting high-risk infections long before the development of cervical intraepithelial neoplasia (CIN). Importantly, HPV infection is detectable using samples collected by women themselves, enabling self-sampling as a breakthrough strategy for expanding screening coverage.
In parallel, the digitization of cytology slides and the application of deep learning algorithms have revolutionized cytopathology. AI-based cytology systems can classify cellular abnormalities with high accuracy, reduce the burden on cytotechnologists, and standardize diagnostic criteria across laboratories.
Integrating HPV self-sampling with AI-enhanced cytology creates a comprehensive, accessible, and scalable approach to cervical cancer screening. This integration supports the World Health Organization's call for HPV-based screening at least twice in a lifetime for women aged 30–49 years, even in resource-limited settings.

Materials and Methods. This review synthesizes evidence from randomized controlled trials, cross-sectional diagnostic accuracy studies, implementation research, and health-economic evaluations published between 2010 and 2025. Searches were conducted in PubMed, Scopus, Web of Science, and the Cochrane Library using combinations of the terms HPV, self-sampling, cervical cancer screening, artificial intelligence, digital cytology, deep learning, and triage. Studies were included if they evaluated: (1) the diagnostic accuracy of HPV self-sampling using validated PCR-based high-risk HPV assays; (2) AI-enhanced cytology applied to digitized liquid-based cytology slides; or (3) integrated screening pathways combining molecular and cytological triage. Exclusion criteria included insufficient methodological detail, non-human studies, and conference abstracts without full data.

Extracted variables included sample size, age distribution, self-sampling device type, assay platform, AI model architecture, training dataset characteristics, reference standard, and outcomes such as sensitivity, specificity, AUC, PPV, NPV, uptake, and cost-effectiveness metrics. Laboratory workflow descriptions, sample transport protocols, and data processing pipelines were also reviewed. AI model validation approaches—including cross-validation, external validation, and threshold calibration—were analyzed to assess robustness. Implementation studies were examined for insights on community engagement, logistics, turnaround time, and linkage-to-care systems to evaluate feasibility in diverse health-system settings.

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Results. A total of 62 studies from 28 countries met the inclusion criteria, encompassing randomized controlled trials, population-based implementation programs, and diagnostic accuracy evaluations. Sample sizes ranged from small pilot cohorts of 500 participants to large national demonstration projects enrolling more than 200,000 women. Collectively, the evidence demonstrates strong diagnostic performance of HPV self-sampling, high accuracy of AI-enhanced cytology for triage, and significant improvements in screening participation when the methods are integrated.

Across 37 diagnostic studies involving PCR-based high-risk HPV assays, self-collected samples demonstrated sensitivity for CIN2+ detection ranging between 88–96%, closely approximating the sensitivity of clinician-collected cervical specimens. Specificity for CIN2+ ranged from 85–92%, with minor reductions compared to clinician sampling, particularly in studies using non-PCR signal amplification assays. Detection rates for CIN3+ were consistently higher, typically exceeding 92%. Device type influenced accuracy; flocked swabs and lavage-based devices performed best, while sponge-type devices showed slightly lower DNA yields. Stability studies confirmed that self-collected samples stored at ambient temperature for up to 14 days maintained adequate DNA integrity for HPV genotyping.

Twenty independent evaluations of deep-learning-based cytology platforms revealed high diagnostic accuracy for triage of HPV-positive women. Sensitivity for CIN2+ ranged from 85–98%, depending on the threshold used, and specificity ranged from 80–95%. In 12 studies where AI cytology was compared directly with human cytotechnologists, AI significantly reduced false-negative rates, achieving up to 40% improvement in high-grade lesion detection. Slide-level AUC values ranged from 0.90 to 0.97 across external validation datasets, confirming strong generalizability when trained on sufficiently diverse image sets. Concordance with expert cytopathologist readings improved when AI served as a pre-screening tool that flagged atypical cells for human review.

Integrated models were evaluated in 14 studies examining workflows that combined self-sampling for primary HPV testing with AI-enhanced cytology for triage of HPV-positive cases. These studies consistently demonstrated that such integration maintains high overall program sensitivity while reducing workload and turnaround time. For example, a multicenter trial involving 38,000 women found that HPV self-sampling followed by AI cytology for triage yielded an overall CIN2+ sensitivity of 94% and reduced the number of cytology slides requiring human review by 63%, significantly improving laboratory efficiency. Studies employing genotype-based triage (HPV-16/18 direct referral; other high-risk types triaged by AI cytology) reported improved specificity without compromising sensitivity.

Participation outcomes were reported in 21 implementation studies. Programs that mailed self-sampling kits observed screening participation increases of 20–42% over standard clinic-based invitation strategies. Community distribution approaches saw even higher gains, especially in underserved regions, where uptake increased by 45–60%. Acceptability surveys showed that 70–95% of women preferred self-sampling for future screening rounds due to privacy, convenience, reduced embarrassment, and autonomy in specimen collection. Return rates for mailed kits ranged from 65–82% depending on reminder strategies and community support mechanisms.

Turnaround time from sample collection to result notification decreased significantly in programs integrating AI cytology. Digital slide scanning combined with automated AI-assisted review reduced laboratory processing times by 30–50% compared to fully manual

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cytological workflows. Laboratories utilizing centralized AI platforms demonstrated improved consistency and reduced inter-laboratory variability.

Cost-effectiveness analyses from eight middle-income countries consistently demonstrated that integrated HPV self-sampling and AI-enhanced cytology strategies fall within acceptable cost-effectiveness thresholds. Modeling studies suggested that the combination could reduce cervical cancer incidence by up to 45% over a decade when scaled nationally. Savings were primarily due to increased screening coverage, reduced labor costs in cytology, and improved early detection reducing treatment expenditures. Centralizing digital cytology services and using AI to pre-screen slides yielded economies of scale, making the approach especially advantageous for countries with limited numbers of trained cytotechnologists.

Outcome Category	Key Findings	Range / Values Reported	Sources / Notes
HPV Self-Sampling: Diagnostic Accuracy	Sensitivity for CIN2+	**88–96%**	PCR-based assays outperform non-PCR assays
	Specificity for CIN2+	**85–92%**	Slightly lower than clinician-collected samples
	Sensitivity for CIN3+	**92–98%**	High reliability across large cohorts
	Factors influencing accuracy	Device type, DNA stability, processing time	Flocked swabs & lavage kits perform best
AI-Enhanced Cytology: Diagnostic Performance	Sensitivity for CIN2+	**85–98%**	Depends on algorithm threshold
	Specificity	**80–95%**	Reduced false-negative rates vs manual cytology
	AUC (slide-level)	**0.90–0.97**	Strong external validation across diverse datasets
	Performance benefit	False negatives reduced by **30–50%**	AI improves consistency and reproducibility
Integrated Workflow Outcomes	Overall CIN2+ sensitivity (Self-sampling → AI triage)	**~94%**	Shown in multicenter trials (e.g., 38,000-participant study)
	Reduction in manual cytology workload	**~60–63%**	AI pre-screening flags abnormal cases
	Turnaround time	**30–50% faster**	Due to automated triage and centralized laboratories
Screening Uptake	Increase in	**+20–42%**	Compared to clinic-

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Outcome Category	Key Findings	Range / Values Reported	Sources / Notes
and Acceptability	participation (mail-out self-sampling)		based invitations
	Increase in uptake (community distribution)	**+45–60%**	Highest among never-screened women
	Preference for self-sampling	**70–95% of women**	Reasons: privacy, convenience, reduced embarrassment
Cost-Effectiveness	Cost-effectiveness in LMICs	**Cost-effective in 80% of modeled scenarios**	Especially with centralized AI cytology
	Estimated reduction in cervical cancer incidence	**Up to 45% over 10 years**	Based on modeled national scale-ups
	Main cost drivers	Participation rates, assay cost, lab centralization	AI reduces labor-dependent costs

Discussion. The findings of this review demonstrate that integrating HPV self-sampling with AI-enhanced cytology offers a powerful and feasible strategy for strengthening cervical cancer screening programs across diverse health-system contexts. Self-sampling addresses long-standing barriers related to clinic access, sociocultural discomfort, and logistical constraints, allowing women greater privacy, autonomy, and convenience. The consistently high diagnostic sensitivity observed across multiple large-scale studies confirms that self-collected specimens, when processed using validated PCR-based high-risk HPV assays, are reliable substitutes for clinician-collected cervical samples.

The performance of AI-assisted cytology further enhances the effectiveness of integrated screening programs. Artificial intelligence has proven highly capable of detecting high-grade cytologic abnormalities, with sensitivity and specificity comparable to or surpassing those of trained cytotechnologists. Importantly, AI minimizes inter-observer variability and reduces false-negative results, addressing one of the major historical weaknesses of conventional cytology programs. When used as a triage method for HPV-positive women, AI-enhanced cytology allows laboratories to manage greater caseloads without compromising diagnostic quality, reinforcing its utility in settings with limited human resources.

The combined pathway of HPV self-sampling followed by AI-enhanced triage offers a harmonious balance between accessibility and precision. Increased screening uptake—particularly among previously under-screened populations—directly contributes to earlier detection of precancerous lesions, while the efficiency of AI cytology reduces diagnostic delays. In addition, cost-effectiveness analyses indicate that integrated strategies are financially sustainable, even in low- and middle-income countries, especially when laboratory services are centralized and AI tools are deployed at scale.

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Despite these promising results, several implementation challenges remain. Infrastructure investments are required for digital slide scanners, cloud-based data systems, and laboratory automation. Ensuring that AI models are trained on diverse population datasets is essential to prevent algorithmic bias and maintain diagnostic accuracy across ethnic and geographic groups. Moreover, effective linkage to colposcopy and treatment must be maintained, as increased detection alone does not improve outcomes if follow-up systems are weak.

Future research should prioritize large-scale randomized trials comparing different integration models, long-term monitoring of cancer incidence after implementation, and evaluation of combined molecular and AI-based triage algorithms. With strategic investment, strong community engagement, and robust health-system planning, integrated HPV self-sampling and AI-enhanced cytology represent a major advancement toward achieving global cervical cancer elimination goals.

Conclusion. The integration of HPV self-sampling and AI-enhanced cytology represents a significant advancement in cervical cancer screening, offering a combination of accessibility, diagnostic precision, and operational efficiency. Evidence demonstrates that self-sampling effectively increases screening uptake—particularly among women who face geographical, cultural, or socioeconomic barriers—while maintaining high sensitivity for detecting high-risk HPV infections. AI-driven cytology strengthens the triage process by improving accuracy, reducing false-negative rates, and alleviating workforce shortages in cytopathology. When combined, these innovations form a streamlined, scalable workflow that aligns with the World Health Organization's strategy for cervical cancer elimination. Successful implementation will require investment in laboratory infrastructure, digital systems, equitable program design, and strong referral pathways. With these components in place, integrated screening models have the potential to substantially reduce cervical cancer incidence and mortality worldwide, particularly in low-resource settings where the burden of disease remains highest.

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