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REVIEW

Emerging Label-Free and Nanoscale Imaging Modalities for Early Detection of Cervical Cancer

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SUMMARY

Cervical cancer remains a major global health challenge, particularly in low- and middle-income countries where organized screening coverage is limited. Current algorithms based on human papillomavirus (HPV) testing and cytology, followed by colposcopy and histopathology, have well-documented limitations in sensitivity, specificity, cost, and turnaround time, and the shift to HPV primary screening has created a large triage population. In parallel, a family of label-free, nanoscale imaging and spectroscopic modalities has matured and is approaching reproducible diagnostic performance: Scanning electron microscopy (SEM) of exfoliated cervical cells, atomic force microscopy (AFM) of cell surface adhesion and mechanical properties, Raman spectroscopy, fluorescence lifetime imaging microscopy, and optical coherence tomography (OCT), coupled to machine learning classifiers. This review describes, discusses, and evaluates current knowledge of these emerging modalities, their diagnostic performance, mechanistic rationale, and readiness for clinical translation. Recent multimodal SEM-AFM pipelines combining discrete wavelet transform-derived features with divergence-based classifiers reached 95.9% classification accuracy; machine learning applied to AFM adhesion maps distinguished precancerous from cancerous cervical cells with an area under the curve (AUC) of 0.93; single-cell Raman spectroscopy with machine learning achieved an AUC of 0.987; and in vivo OCT reached 93.4% accuracy for high-grade lesions, with OCT triage after HPV genotyping reaching an AUC of 0.921. Implementation evidence for HPV self-sampling, the likely specimen source for nanoscale approaches, is also reviewed. The remaining barriers, including small cohorts, absent prospective validation, protocol standardization, and instrumentation cost, are analyzed, and a roadmap toward integration of these biomarkers into risk-based screening programs is proposed.

Keywords: Early detection of cancer; electron, machine learning; mass screening, microscopy, scanning; uterine cervical neoplasms.

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INTRODUCTION

Cervical cancer is a preventable malignancy whose global burden remains concentrated in low- and middle-income countries, and the World Health Organization elimination strategy rests on vaccination, screening, and timely treatment of precancerous lesions.[1] Organized screening based on the Papanicolaou smear, later augmented by liquid-based cytology, automation, human papillomavirus (HPV) primary testing, geno-

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typing, and dual-stain triage, has driven substantial reductions in incidence in high-income settings.[2] HPV vaccination is now reshaping screening paradigms further, with longer intervals and risk-based algorithms replacing uniform cytology-based recall.[3]

Nevertheless, the current gold standard pathway, HPV testing and cytology for screening followed by colposcopy and histopathology for diagnosis, is limited in sensitivity and specificity, is costly and time-consuming, and depends on laboratory and colposcopy capacity that is unevenly distributed worldwide.[4] In premenopausal and older women, epithelial atrophy and migration of the transformation zone into the endocervical canal reduce the sensitivity of conventional cytology, a problem highlighted in recent morphometric and ultrastructural studies of precancerous cervical lesions.[5] These gaps motivate complementary, ideally label-free and minimally invasive, modalities for early detection.

This review describes, discusses, and evaluates the current level of knowledge of a family of emerging, high-resolution imaging and spectroscopic modalities for early cervical cancer detection: Scanning electron microscopy (SEM) and atomic force microscopy (AFM) of exfoliated cervical cells, their multimodal machine learning-assisted combinations, adjacent label-free platforms (Raman spectroscopy, Fluorescence lifetime imaging microscopy [FLIM]), and, as the most clinically advanced optical counterpart, OCT and related endomicroscopic imaging. Because the exfoliated cell is the common specimen of this literature and its collection is being transformed by HPV self-sampling, the implementation evidence for self-sampling is reviewed first, followed by the technology-specific sections. The focus throughout is on diagnostic performance, mechanistic rationale, and readiness for clinical translation.

THE CURRENT SCREENING PATHWAY AND ITS LIMITATIONS

The modern cervical screening algorithm has evolved from the conventional Pap smear through liquid-based cytology and automation to HPV primary screening with cytology triage of HPV-positive women, and most recently to digitalization and artificial intelligence (AI) assistance.[2] In many contemporary programs, HPV testing is now the primary test and cytology is used mainly for triage of HPV-positive women.[6] This shift has improved sensitivity for high-grade lesions but has created a large pool of HPV-positive women requiring triage, increasing the workload of cytology laboratories and colposcopy clinics.[6]

Three specific limitations of the current pathway create space for emerging modalities. First, cytology remains labor-intensive and subject to interobserver variability.[6] Second, HPV testing alone has imperfect specificity, particularly in younger women, and triage markers such as genotyping and dual staining are being introduced to personalize management.[2] Third, in specific clinical scenarios such as the premenopausal period with atrophic epithelial changes, conventional cytology loses sensitivity, and advanced morphometric and ultrastructural methods have been proposed to bridge this diagnostic gap.[5]

HPV SELF-SAMPLING: THE SPECIMEN PIPELINE FOR CELL-BASED TECHNOLOGIES

Cell-based nanoscale and spectroscopic modalities depend on the availability of exfoliated cervical cells, and the collection step is itself undergoing transformation. Self-sampling for HPV testing is now recommended by the World Health Organization, and a systematic review and meta-analysis of six trials involving 29,018 participants in low- and middle-income countries found a small but significant improvement in screening uptake with self-sampling versus provider collection (risk ratio [RR] 1.11, 95% confidence interval [CI] 1.10–1.11), which increased to RR 1.82 (95% CI 1.67–1.99) in a sensitivity analysis of five trials with harmonized uptake definitions.[7] In the United States, the phase 3 MBMT-3 randomized trial showed that mailed HPV self-collection kits with appointment-scheduling assistance increased screening uptake among under-screened low-income women from 37% to 72% (RR 1.93, 95% CI 1.62–2.31).[8] In an internet-based program in China, 20,136 women performed vaginal self-sampling for HPV testing, 95.97% of respondents reported that self-sampling was easy to perform, and the model reached under-screened and remote populations effectively.[9] Self-collected vaginal samples showed HPV positivity statistically similar to provider-collected samples in a Zimbabwean crossover study (26.9% vs. 29.3%), supporting diagnostic comparability.[10]

Acceptability and cost data reinforce these findings. Community-based distribution achieves 20–35% uptake in resource-limited settings while reducing costs by 32–48%, and vaginal brushes achieve a sensitivity of 94.6% (95% CI 92.4–96.8) for HPV detection.[11] In India, HPV self-sampling showed 97% acceptance in urban slum settings with 95.1%

agreement between self-collected and health-worker-collected samples, and pictorial instructions performed as well as personnel-delivered education.[12] A critical review concluded that self-sampling improves participation among women hesitant to attend facility-based screening and reduces provider burden, while noting that best practices for target populations and follow-up protocols remain to be established.[13] Implementation science is catching up: a stakeholder-engaged pre-implementation study in rural China specified four strategy packages for village doctor-delivered self-sampling, and in its pilot, 62.2% of 172 invited women completed self-sampling with 99.1% of samples meeting testing standards.[14] For nanoscale imaging technologies, this evidence is strategically important: self-collected specimens could feed SEM, AFM, and spectroscopic pipelines, extending their reach beyond clinic-based populations, although cell quality and pre-analytical standardization from self-sampling devices require dedicated validation.[11,13]

SEM OF EXFOLIATED CERVICAL CELLS

SEM provides nanometer-scale imaging of the surface ultrastructure of exfoliated cervical cells, including microvilli and surface projections whose density and morphology change during carcinogenesis. Recent work has moved beyond descriptive ultrastructure toward quantitative, computational classification: in a multimodal study, 540 SEM and 540 AFM cell images were analyzed using discrete wavelet transform (DWT)-derived features and three divergence-based classifiers (triangle divergence, Jensen-Shannon divergence, and Hellinger divergence), with feature likelihoods combined using exponential graph regulation.[15] The combined SEM-AFM approach with triangle divergence achieved a classification accuracy of 95.9% for distinguishing normal, benign, and malignant cells, outperforming single-modality analysis.[15]

In a related study applying 16 DWT families (Daubechies, Coiflet, Symlet, and Biorthogonal) to SEM and AFM images of cervical cells, the average classification rates were 98.29% for AFM images and 97.10% for SEM images, with ten texture features calculated for each approximation and detail coefficient.[16] The surface roughness of malignant AFM images was larger than that of normal and benign images, whereas the volume of particles in malignant AFM images was smaller.[16] These studies demonstrate that quantitative texture features of cell surface ultrastructure carry discriminative information, although the cohorts remain small and the imaging workflow requires specialized infrastructure.[15,16]

AFM: ADHESION, MECHANICS, AND FRACTAL ANALYSIS

AFM provides nanoscale topographic, adhesive, and mechanical mapping of individual cells. A key advance was the use of high-resolution AFM adhesion maps: analysis of adhesion between the AFM probe and the cell surface allowed discrimination of normal from cancerous or precancerous cervical epithelial cells using a single parameter, fractal dimension, and subsequent introduction of machine learning (random forest) improved the separation of precancerous from cancerous cells to an area under the curve (AUC) of 0.93, with accuracy, sensitivity, and specificity of 83%, 92%, and 78%, respectively.[17] Because the separation between premalignant and malignant cells is the most clinically significant distinction, the improvement in sensitivity was emphasized as clinically meaningful, and the authors proposed that relatively low specificity could be compensated by combining this approach with existing screening methods.[17]

Mechanical phenotyping is a parallel line of evidence. AFM force-indentation measurements fitted with Hertz and Sneddon models, complemented by stress-relaxation analysis, have shown that elastic and viscoelastic properties of cancer cells, including cervical cancer cells, are lower than those of normal cervical and mammary epithelial cells, and that measured properties depend on probe geometry, tip radius, and loading rate.[18] These findings confirm that biomechanical fingerprints are reproducible and quantifiable, but also that measurement protocols must be standardized for clinical use.[18] Instrument-side progress continues: an adaptive harmonic AFM probe generated stable harmonic signals in atmospheric and liquid environments and improved classification accuracy for normal versus cancer cervical cells by approximately 8% and between HeLa and SiHa cancer subtypes by approximately 13%, using 3,600 cell samples.[19]

MULTIMODAL SEM-AFM PIPELINES AND MACHINE LEARNING

The convergence of SEM and AFM with computational feature extraction represents the most recent method-

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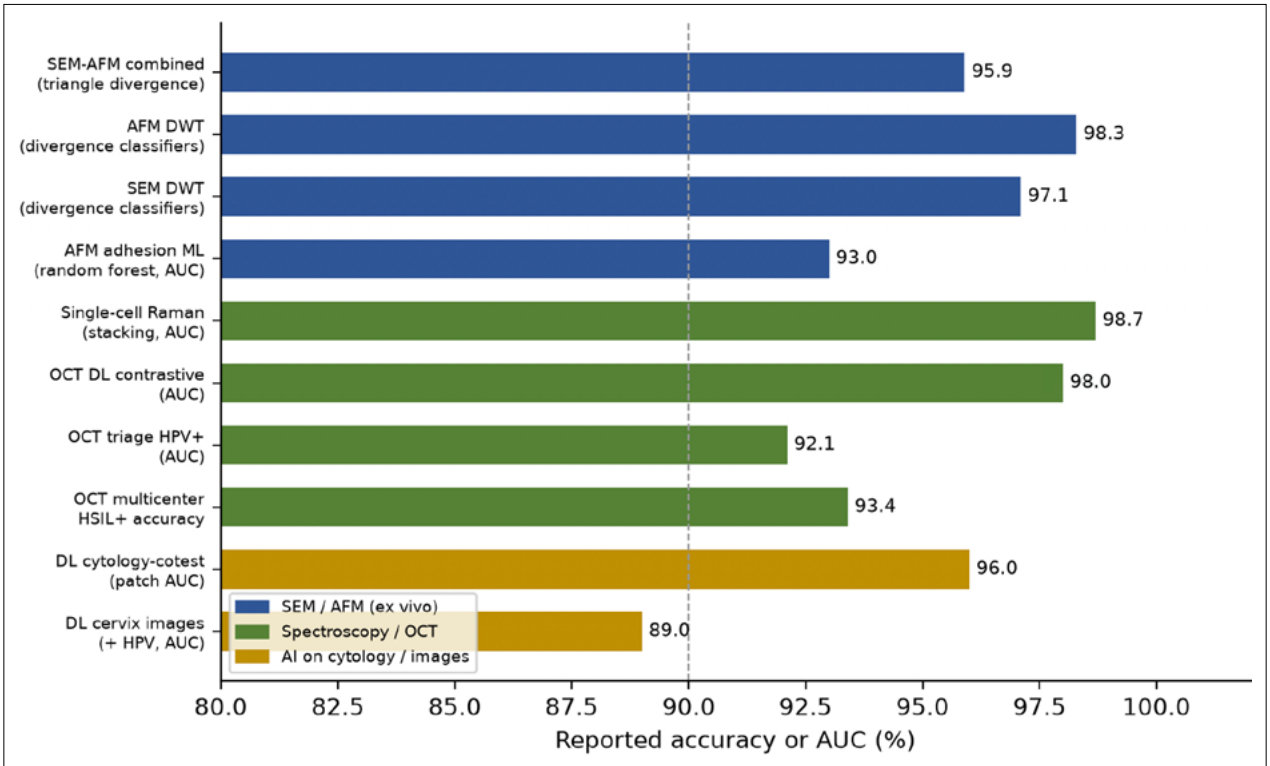


Fig. 1. Reported classification accuracy or area under the curve of the modalities reviewed, grouped by modality family. Values are as reported in the primary studies and are not directly comparable across cohorts.

ological step. The multimodal DWT-divergence pipeline categorized SEM and AFM cells into six groups (normal, benign, and malignant for each modality) and demonstrated that the weighted combination of features improved diagnostic precision over either modality alone.[15] The rationale is that SEM captures surface architecture while AFM captures nanomechanical and adhesive properties, so their combination reduces the diagnostic unreliability inherent in relying on a single imaging technique.[15]

Machine learning is the common denominator across these pipelines. Beyond the divergence-based classifiers of the SEM-AFM studies,[15,16] random forest models applied to AFM adhesion maps achieved an AUC of 0.93 for precancerous versus cancerous discrimination,[17] and unsupervised machine learning applied to FLIM images of exfoliated cells achieved a sensitivity of 90.9% and specificity of 100% for cervical cancer risk prediction, outperforming cytology in the same study.[20] Single-cell Raman spectroscopy combined with seven machine learning algorithms, with a stacking ensemble selected as optimal, achieved an AUC of 0.987, accuracy of 99.2%, sensitivity of 98.9%, and specificity of 99.3% for distinguishing normal from abnormal cervical exfoliated cells.[21] Figure 1 compares the reported classification performance across these modalities, and the proposed multimodal pipeline integrating them is shown in Figure 2. These results, although generated in pilot and single-center settings, establish that label-free nanoscale and spectroscopic data streams are amenable to reproducible computational classification.[15,17,20,21]

ADJACENT LABEL-FREE MODALITIES: RAMAN SPECTROSCOPY AND FLIM

Raman spectroscopy provides molecular fingerprints of tissue and exfoliated cells without labels and has been studied for cervical cancer detection for over two decades using exfoliated cells, biofluids, and tissue *ex vivo* and *in vivo*.[4] A recent pilot multimodal study combined Raman spectroscopy with AFM and SEM on paraffin-embedded cervical squamous cell carcinoma samples, identifying distinct molecular profiles between malignant and healthy tissue regions in the 813–1668 cm−1 range, with AFM and SEM providing supportive morphological

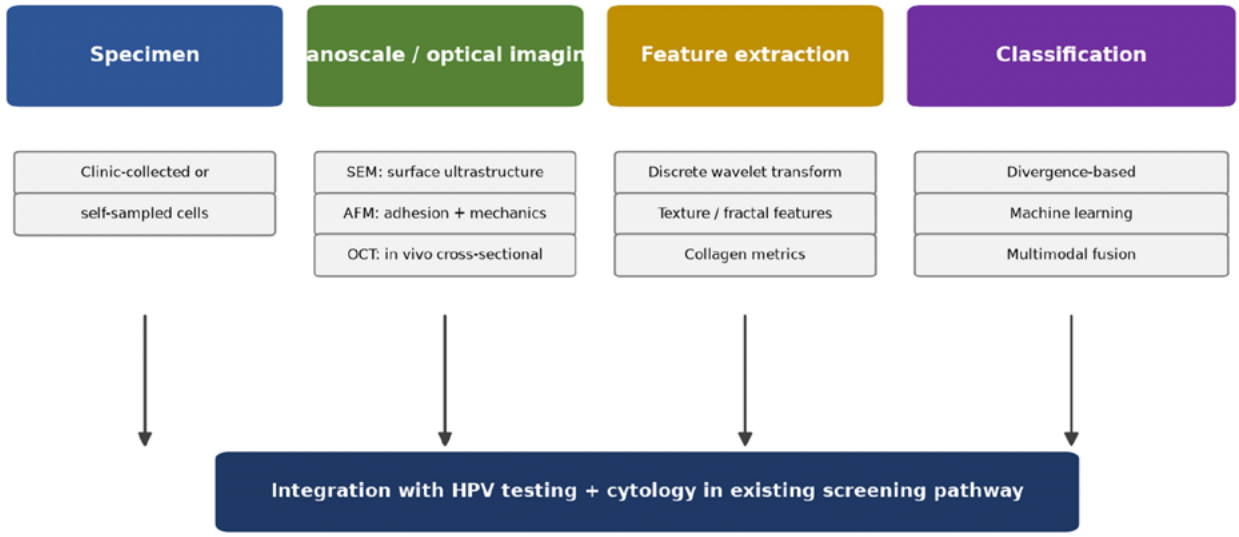


Fig. 2. Proposed multimodal pipeline for early detection of cervical cancer, from specimen collection through nanoscale/optical imaging and feature extraction to classification and integration with the existing screening pathway.

information on structural irregularities associated with malignancy.[22] The authors emphasized that Raman spectroscopy has not yet replaced Pap smears and biopsies in clinical practice due to challenges in standardization, reproducibility, and clinical validation, positioning the multimodal approach as a stepping stone toward minimally invasive, label-free diagnostic workflows.[22]

FLIM, by measuring endogenous NAD(P)H fluorescence lifetime, captures metabolic state changes in exfoliated cervical cells. Combined with unsupervised machine learning, FLIM images from 71 participants yielded a sensitivity of 90.9% and specificity of 100% for cervical cancer risk prediction, significantly higher than cytology, and one cancer recurrence case was flagged months earlier than by current clinical methods.[20] Complementing these optical approaches, single-cell transcriptomic profiling of cervical exfoliated cells has identified molecular biomarkers of progression, including a lipid-associated macrophage subset that predicted progression from low-grade to high-grade squamous intraepithelial lesion (HSIL) and an SPP1-CD44 protumor signaling axis between epithelial cells and macrophages, verified by immunofluorescence.[23] Together, these modalities illustrate a converging trend: the exfoliated cervical cell can now be interrogated at nanoscale, metabolic, and single-cell transcriptomic levels, each yielding quantitative biomarkers of carcinogenesis.[20,22,23]

OPTICAL COHERENCE TOMOGRAPHY AND ENDOMICROSCOPY: THE *IN VIVO* FRONTIER

OCT is the most clinically advanced *in vivo* counterpart to the *ex vivo* nanoscale modalities, providing non-invasive, real-time, cross-sectional imaging of cervical epithelium and stroma. In a multicenter study of 1,214 patients with cervical lesions examined by *in vivo* OCT, the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of OCT for diagnosing HSIL or worse (HSIL+) were 93.4%, 88.5%, 95.0%, 85.0%, and 96.2%, respectively, with strong consistency with histopathology (kappa 0.701); for low-grade lesions, the corresponding values were 84.7%, 61.7%, 96.3%, 89.3%, and 83.2%.[24] In the same study, OCT screening outperformed combined HPV and ThinPrep cytologic test screening, with accuracy 83.7% versus 64.9%, sensitivity 77.8% versus 64.5%, and specificity 91.8% versus 65.4% (all $p<0.001$).[24] Figure 3 presents these diagnostic metrics.

OCT also functions as a triage tool. In a cross-sectional study of 883 women referred for colposcopy, HPV combined with OCT showed higher specificity for detecting CIN2+ and CIN3+ than HPV combined with cytology (96.1% vs. 93.2%, $p=0.002$; 93.8% vs. 91.3%, $p=0.013$), and OCT triage after HPV genotyping achieved the highest AUC for detecting CIN2+ and CIN3+ among women with high-risk HPV infection (0.921 and 0.920, respectively).[25] Figure 4 summarizes this triage evidence. AI is being layered

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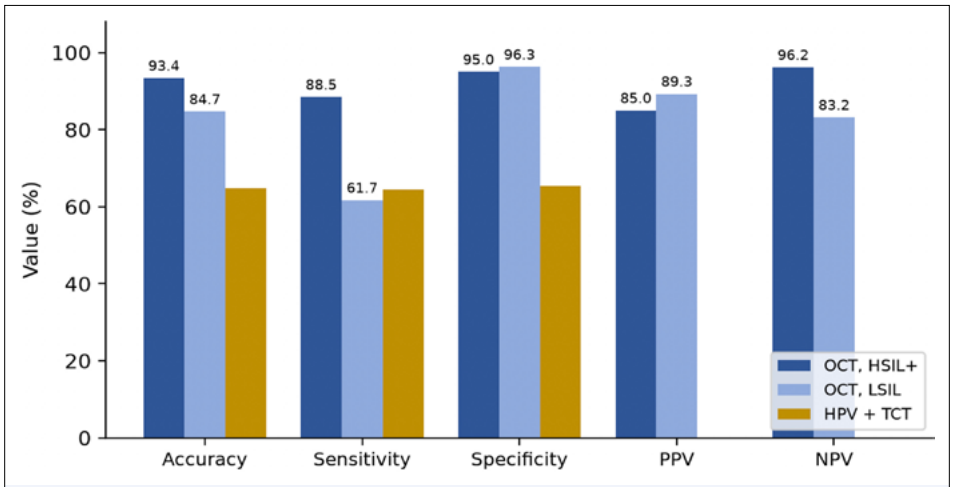


Fig. 3. Diagnostic metrics of *in vivo* optical coherence tomography for high-grade squamous intraepithelial lesion + and low-grade squamous intraepithelial lesion versus combined human papillomavirus and ThinPrep cytologic test screening in the multicenter study. Positive predictive value and negative predictive value for the combined screening arm were not reported.

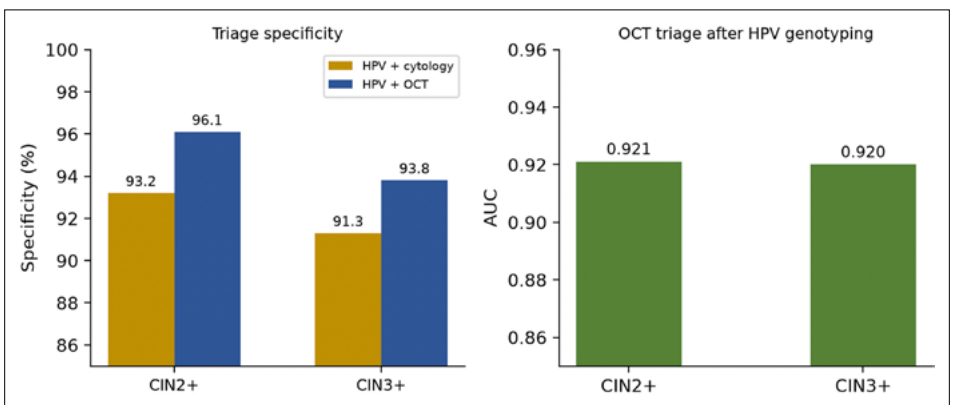


Fig. 4. Optical coherence tomography (OCT) as a human papillomavirus (HPV) triage tool: Specificity of HPV combined with OCT versus HPV combined with cytology (left) and area under the curve of OCT triage after HPV genotyping (right).

onto OCT rapidly: A contrastive self-supervised texture learning model achieved an AUC of 0.98 for detecting high-risk lesions on OCT image patches, with 91.5% sensitivity and 97.4% specificity on an external validation set of 287 three-dimensional OCT volumes from 118 patients,[26] and a feature-pyramid deep learning model achieved F1-scores of 81.6% and 84.3% on two clinical datasets, outperforming five experienced medical experts on one.[27]

Technology development continues along three fronts. Probe-based quantitative OCT of collagen fiber organization, using an extended-depth-of-focus quasi-Bessel beam, produced a tumor potential index map that merges multiple metrics to guide biopsy targeting in *ex vivo* human specimens and *in vivo* murine models.[28] Gabor-domain optical coherence microscopy achieved near-histologic resolution of cervical dysplasia *ex vivo*, resolving epithelium, stroma, basement membrane, and HPV-associated changes,[29] and high-resolution optical coherence microscopy has been applied to endocervical canal lesions, addressing a structure poorly visualized by conventional screening.[30] Endoscopic OCT combined with autofluorescence imaging is being evaluated for *in vivo* endocervical canal imaging,[31] and OCT has also been used to map tissue architecture and extracellular matrix abnormalities in human cer-

vix specimens.[32] At the implementation level, a low-cost multiscale system combining portable colposcopy with high-resolution endomicroscopy, coupled to a multiscale imaging fusion network, achieved sensitivity equal to clinical impression (0.98) with significantly higher specificity (0.75 vs. 0.43, p=0.000006), demonstrating that accurate real-time diagnosis of high-grade pre-cancers is feasible in low-resource settings.[33]

AI IN CERVICAL SCREENING AND THE PLACE OF NANOSCALE IMAGING

AI is already reshaping cervical screening through digital cytology, automated image analysis, and colposcopy support.[6,34] Model-based evaluation of AI-assisted digital cytology within the National Health Service (NHS) cervical screening program estimated that reviewing and reporting 479,125 slides annually would require 31,842 staff hours with AI-assisted digital cytology versus 103,151 h with manual microscopy, corresponding to a potential 69% increase in overall productivity.[35] In a clinical evaluation of an AI-assisted cytology system in a high-risk Chinese population, the AI strategy achieved the highest Youden index at both low-grade and HSIL thresholds and outperformed liquid-based cytology plus HPV cotesting at the high-grade threshold.[36] A proof-of-concept deep learning model applied to digitized ThinPrep cytology and HPV cotest results achieved an image-patch-level AUC of 96% in temporal validation, although prospective multicenter studies with patient-level analysis were deemed necessary before clinical implementation.[37]

For low- and middle-income settings, portable AI-assisted devices such as smartphone colposcopes with embedded deep learning have demonstrated CIN2+ sensitivities above 90%, exceeding expert readers, and deep learning pipelines trained on large multi-institutional cervical image datasets (9,462 women, 17,013 images) reached an AUC of 0.89 when combined with HPV type, with an extreme misclassification rate of 3.4% on held-aside test sets.[34,38] These developments are directly relevant to SEM-, AFM-, and OCT-based screening because the computational infrastructure, feature extraction methods, and validation frameworks developed for cytology and colposcopy images are transferable to nanoscale imaging modalities.[6,15] Conversely, the challenges identified for AI in cervical screening, including algorithmic bias from non-representative training data, limited interpretability, regulatory uncertainty, and the need for large, diverse datasets and prospective validation,[6,34] apply equally to machine learning applied to SEM, AFM, and OCT data.[17,15,26]

COMPARATIVE EVALUATION AND CLINICAL TRANSLATION

Table 1 summarizes the diagnostic performance of the modalities reviewed, and Figure 1 compares their reported classification performance. Three observations follow. First, the reported accuracies of SEM-AFM, spectroscopic, and OCT pipelines (approximately 93–99%) are higher than those typically reported for cytology or HPV testing alone, but they derive from small, single-center, and frequently retrospective cohorts, and no head-to-head comparison of SEM-AFM or AFM with HPV testing within a single screening population has been published; by contrast, OCT has now been compared directly against combined HPV-cytology screening in a multicenter cohort and outperformed it.[15–17,20,21,24] Second, the mechanistic rationale is strong and convergent: malignant transformation alters surface ultrastructure, adhesion, mechanical compliance, metabolic state, and stromal collagen organization, and each modality captures a different aspect of these changes.[16,18,22,20,28] Third, multimodal designs consistently outperform single-modality analysis, whether SEM with AFM,[15] Raman with AFM and SEM,[22] widefield colposcopy with endomicroscopy,[33] or HPV genotyping with OCT,[25] supporting a multimodal architecture for future clinical studies (Fig. 2).

The practical barriers to clinical translation are consistent across modalities: the need for prospective validation in diverse populations,[6,37] standardization of sample preparation and imaging protocols,[5,18] the cost and infrastructure requirements of SEM and AFM instrumentation in screening settings,[15,16] and the interpretability and regulatory questions that apply to any machine learning-based diagnostic.[6,34] OCT, by contrast, is already *in vivo*, real-time, and comparatively low-cost, and its multicenter performance data position it closest to clinical adoption.[24,25] A realistic near-term pathway is therefore not replacement of HPV-based screening but targeted integration: Nanoscale and spectroscopic modalities are best positioned as triage tools for HPV-positive women or as adjuncts in specific scenarios, such as premenopausal women with atrophic epithelium where conventional cytology loses sensi-

Table 1 Diagnostic performance of emerging label-free, nanoscale, and AI-assisted modalities for early detection of cervical cancer

Modality	Sample	Classifier/analysis	Reported performance	Key evidence
Multimodal SEM-AFM	540 SEM+540 AFM cervical cell images	DWT features; triangle divergence; exponential graph regulation	Accuracy 95.9% (combined)	[15]
SEM (single modality)	SEM cervical cell images	16 DWT families; divergence-based classifiers	Classification rate 97.10%	[16]
AFM (single modality)	AFM cervical cell images	16 DWT families; divergence-based classifiers	Classification rate 98.29%	[16]
AFM adhesion maps	Precancerous and cancerous primary cervical cell lines	Random forest on high-resolution adhesion maps	AUC 0.93; accuracy 83%; sensitivity 92%; specificity 78%	[17]
Adaptive harmonic AFM	3,600 cervical epithelial and cancer cells	Adaptive harmonic probe; cellular classification	Classification accuracy improved by 7.97% (normal vs. cancer); 12.73% (HeLa/SiHa)	[19]
Single-cell Raman spectroscopy	128 cervical exfoliated cell samples	Stacking ensemble of 7 machine learning algorithms	AUC 0.987; accuracy 99.2%; sensitivity 98.9%; specificity 99.3%	[21]
FLIM of exfoliated cells	71 participants	Unsupervised machine learning on NAD(P)H lifetime	Sensitivity 90.9%; specificity 100%	[20]
In vivo OCT (multicenter)	1,214 patients with cervical lesions	Image interpretation versus histopathology	HSIL+: accuracy 93.4%; sensitivity 88.5%; specificity 95.0%; NPV 96.2%	[24]
OCT versus HPV+TCT screening	Same multicenter cohort	OCT versus combined HPV-cytology screening	Accuracy 83.7% versus 64.9%; specificity 91.8% versus 65.4%	[24]
OCT triage after HPV genotyping	883 women referred for colposcopy	OCT combined with HPV genotyping	AUC 0.921 (CIN2+); 0.920 (CIN3+); specificity gain over HPV+cytology	[25]
OCT deep learning (contrastive)	733 patients; external validation 118 patients	Contrastive self-supervised texture learning	AUC 0.98; external sensitivity 91.5%; specificity 97.4%	[26]
OCT deep learning (FPN)	Two clinical datasets	Feature pyramid network with texture encoding	F1 81.6% and 84.3%; outperformed 5 of 5 and matched best expert	[27]
AI-assisted digital cytology	NHS cervical screening program workflow	Decision-tree model of AI-assisted digital cytology	31,842 versus 103,151 staff hours; potential 69% productivity increase	[35]
AI-assisted cytology (clinical)	1,231 LBC slides, high-risk Chinese population	AI-assisted cytological system	Best Youden index at LSIL and HSIL+ thresholds; AUC 0.621 at HSIL+	[36]
Deep learning on cytology-cotest	337 women, temporal validation cohort	ResNet50 ensemble on digitized ThinPrep slides	Patch-level AUC 96% in temporal validation	[37]
Deep learning cervix images+HPV	9,462 women; 17,013 images	Multi-institutional deep learning pipeline	AUC 0.89; extreme misclassification 3.4%	[38]
Smartphone colposcope AI	Low-resource settings	Embedded deep learning on smartphone colposcopy	CIN2+ sensitivity >90%, exceeding expert readers	[34]

SEM: Scanning electron microscopy; AFM: Atomic force microscopy; DWT: Discrete wavelet transform; AUC: Area under the curve; FLIM: Fluorescence lifetime imaging microscopy; NAD(P)H: Reduced nicotinamide adenine dinucleotide (phosphate); LBC: Liquid-based cytology; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; CIN2+/CIN3+: Cervical intraepithelial neoplasia grade 2/3 or worse; HPV: Human papillomavirus; TCT: ThinPrep cytologic test; NPV: Negative predictive value; PPV: Positive predictive value; NHS: National Health Service.

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Table 2 Diagnostic performance of *in vivo* OCT in a multicenter study of 1,214 patients (pathology as gold standard)

Metric	OCT, HSIL+ (%)	OCT, LSIL (%)	HPV+TCT combined screening (%)
Accuracy	93.4	84.7	64.9
Sensitivity	88.5	61.7	64.5
Specificity	95.0	96.3	65.4
Positive predictive value	85.0	89.3	-
Negative predictive value	96.2	83.2	-

HPV+TCT values from the same multicenter comparison; PPV and NPV not reported for the combined screening arm. PPV: Positive predictive value; NPV: Negative predictive value; HPV: Human papillomavirus; OCT: Optical coherence tomography; HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion.

tivity [5] and post-treatment follow-up where metabolic imaging showed early recurrence detection.[20] Self-sampling evidence suggests a further integration point: coupling self-collected specimens to label-free cell analysis could extend triage capacity to under-screened populations[7–9,11] (Table 2, 3, Fig. 5).

Limitations and Future Directions

The evidence base for SEM- and AFM-based early detection of cervical cancer remains preliminary. Sample sizes are small, most studies are retrospective, and external validation is lacking.[5,15–17] Reported accuracies may be inflated by dataset-specific feature engineering and by the absence of blinded, consecutive, screening-population sampling.[15,16] Standardization of cell preparation, fixation, imaging parameters, and feature extraction is not established, which impedes comparison across studies.[5,18] For OCT, multicenter evidence is stronger but remains confined to referral populations, and OCT performance for low-grade lesions is modest (sensitivity 61.7%), limiting its standalone use.[24] The regulatory pathway for machine learning-based diagnostics using nanoscale imaging data is not defined.[6,34] Finally, the cost and throughput of SEM and AFM are not yet compatible with population-scale screening, and the technology may realistically enter clinical practice first in research and specialized diagnostic settings.[15,19]

Future studies should prioritize: (1) Prospective, multicenter, blinded validation of SEM-AFM and spectroscopic pipelines against histopathological endpoints in consecutive screening populations; (2) head-to-head comparison with HPV testing and cytology within the same cohort, mirroring the multicenter OCT design;[24] (3) development of standardized operating procedures for sample preparation and imaging, including for self-collected specimens;[10,11,18]; (4) integration of nanoscale imaging data with HPV status and cytology in multimodal machine learning models;[25,37,38] and (5) exploration of cost-effective AFM, Raman, and OCT configurations suitable for point-of-care or low-resource deployment, building on the portable colposcopy-endomicroscopy experience.[33,34] If these steps are taken, nanoscale and spectroscopic modalities could mature from promising research tools into complementary components of risk-based cervical screening programs.

Table 3 Evidence for HPV self-sampling as the specimen pipeline for cell-based technologies

Study	Setting/population	Design	Key finding
Mekuria et al.[7]	LMICs; 6 trials, 29,018 participants	Systematic review and meta-analysis	Uptake RR 1.11 (95% CI 1.10–1.11); RR 1.82 (95% CI 1.67–1.99) in sensitivity analysis
Pretsch et al.[8]	Under-screened low-income women, USA	Phase 3 randomized controlled trial (MBMT-3)	Uptake 72% versus 37%; RR 1.93 (95% CI 1.62–2.31)
Li et al.[9]	13 provinces, China; 20,136 women	Internet-based self-sampling program	95.97% found self-sampling easy; reached remote and under-screened women
Munjoma et al.[10]	Zimbabwe; 609 self-versus 611 provider samples	Cross-sectional crossover trial	HPV positivity 26.9% versus 29.3%; statistically similar
Gomes et al.[11]	Global review across healthcare settings	Narrative review	Vaginal brush sensitivity 94.6%; cost reduction 32–48%; uptake 20–35%
Anand et al.[12]	Urban slum settings, India	Cross-sectional acceptability study	97% acceptance; 95.1% agreement with health-worker samples
Wang et al.[14]	Rural China; 172 invited women	Pre-implementation implementation science study	62.2% completed self-sampling; 99.1% samples met testing standards

HPV: Human papillomavirus; RR: Risk ratio; CI: Confidence interval; LMICs: Low- income countries.

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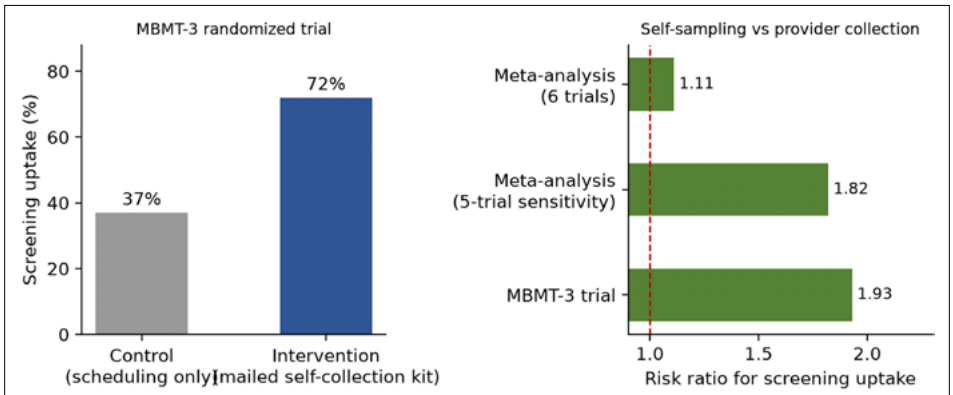


Fig. 5. Human papillomavirus self-sampling evidence: screening uptake in the MBMT-3 randomized trial (left) and risk ratios for uptake with self-sampling versus provider collection (right).

CONCLUSION

Emerging label-free modalities, SEM and AFM of exfoliated cervical cells, their multimodal and machine learning-assisted combinations, adjacent spectroscopic and metabolic imaging platforms, and *in vivo* OCT with its AI-assisted analysis, have reached sufficient diagnostic performance to justify rigorous clinical evaluation for early detection of cervical cancer. Multimodal SEM-AFM pipelines have achieved accuracies of approximately 96%; machine learning on AFM adhesion maps has distinguished precancerous from cancerous cells with an AUC of 0.93; single-cell Raman spectroscopy combined with machine learning has reached an AUC of 0.987; and *in vivo* OCT has reached 93.4% accuracy for high-grade lesions, with demonstrated superiority over combined HPV-cytology screening and an AUC of 0.921 as an HPV triage tool. The remaining barriers are not conceptual but logistical and regulatory: prospective validation, standardization, and cost-effective deployment. The most realistic path to clinical impact is targeted integration into existing HPV-based screening algorithms as a triage or adjunct tool, with self-sampling programs supplying the specimen pipeline, rather than replacement of established tests, and the framework proposed here, multicenter prospective validation, standardized protocols, and multimodal model development, is intended to guide the next phase of studies in this field.

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REFERENCES

1. Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, et al. Breast cancer: pathogenesis and treatments. Signal Transduct Target Ther 2025;10:49.
2. Kholová I, Booth CN, Edvardsson H, Nayar R, Negri G, Pantanowitz L. The development path of gynecological cytology after papanicolaou: from bethesda to artificial intelligence and personalized medicine. Acta Cytol 2026:1–13.
3. Galani A, Zikopoulos A, Moustakli E, Potiris A, Paraskevaidi M, Arkoulis I, et al. Cervical cancer screening in the hpv-vaccinated and digital era: reassessing strategies in light of artificial intelligence and evolving risk. Cancers (Basel) 2025;17:3179.
4. Shaikh R, Daniel A, Lyng FM. Raman spectroscopy for early detection of cervical cancer, a global women's health issue-a review. Molecules 2023;28:2502.
5. Reymnazarova GD, Asatulaev AF, Magrupov BA. Morphological and functional diagnosis of precancerous cervical lesions in premenopausal women using advanced diagnostic methods. Innov Med Kuban 2026;11:88–96.
6. Stanek-Widera A, Borowczak J, Skiba D, Mickael ME, Łazarczyk M, Maniewski M, et al. Artificial intelligence in cervical cytology: opportunities and limitations in screening, triage, and diagnostic support. Diagnostics (Basel) 2026;16:1541.

7. Mekuria SF, Timmermans S, Borgfeldt C, Jerkeman M, Johansson P, Linde DS. HPV self-sampling versus healthcare provider collection on the effect of cervical cancer screening uptake and costs in LMIC: a systematic review and meta-analysis. Syst Rev 2023;12:103.
8. Pretsch PK, Spees LP, Brewer NT, Hudgens MG, Sanusi B, Rohner E, et al. Effect of HPV self-collection kits on cervical cancer screening uptake among under--screened women from low-income US backgrounds (MBMT-3): a phase 3, open-label, randomised controlled trial. Lancet Public Health 2023;8:e411–e21.
9. Li J, Wu R, Qu X, Huang X, Li L, Lin Z, et al. Effectiveness and feasibility of self-sampling for human papillomavirus testing for internet-based cervical cancer screening. Front Public Health 2022;10:938272.
10. Munjoma M, Gudukeya S, Mavudze J, Chipfumbu C, Madzivire D, Madidi N, et al. Feasibility and acceptability of HPV DNA self-sampling in a low-resource setting. Cancer Plus 2025;7:47–60.
11. Gomes M, Provaggi E, Pembe AB, Olaitan A, Gentry-Maharaj A. Advancing cervical cancer prevention equity: innovations in self-sampling and digital health technologies across healthcare settings. Diagnostics (Basel) 2025;15:1176.
12. Anand KV, Mishra G, Pimple S, Biswas S, Kulkarni V, Salunke G. Cross-sectional study of HPV self-sampling among Indian women: a way forward. Indian J Med Paediatr Oncol 2022.
13. Mishra A, Chadha S. A critical review of human papillomavirus self-sampling: evidence and impact. J Colposcopy Lower Genital Tract Pathol 2025;3:48–53.
14. Wang Q, Lingqing Q, Da X, Ma J, Qi S, Ren H, et al. Developing implementation strategies for village doctor-delivered HPV self-sampling in rural cervical cancer screening: a rapid, stakeholder-engaged pre-implementation study using the implementation research logic model. Implement Sci Commun 2026.
15. Ozbey G, Aytac S. A multimodal scanning electron microscopy-atomic force microscopy images for early cervical cancer detection using discrete wavelet transform-derived features and divergence-based classification. Rev Assoc Med Bras 2026;72:e20251173.
16. Aytaç S, Özbey G. Photodiagnosis and photodynamic recognition of cervical cancer with SEM and AFM images. PLoS One 2025;20:e0316544.
17. Petrov M, Sokolov I. Machine learning allows for distinguishing precancerous and cancerous human epithelial cervical cells using high-resolution AFM imaging of adhesion maps. Cells 2023;12:2536.
18. Wang L, Deng W, Zhang C, Liu R, Chen W, Liu X. Single cell biomechanical properties analyzed by atomic force microscopy. Research Square 2025.
19. Feng K, Yuan L, Zhang X. An adaptive harmonic AFM probe with enhanced sensitivity for cellular imaging. Appl Phys Lett 2025;127:033701.
20. Ji M, Zhong J, Xue R, Su W, Kong Y, Fei Y, et al. Early detection of cervical cancer by fluorescence lifetime imaging microscopy combined with unsupervised machine learning. Int J Mol Sci 2022;23:11476.
21. Ma D, Zhao W, Liu S, Xu H, Cai D, Ji Y, et al. Establishment and assessment of an early screening model for cervical cancer based on single-cell Raman spectroscopy combined with machine learning algorithms. Journal of Precision Medicine 2025;40:348–52.
22. Proietti A, De Angelis E, Buccini L, Leopizzi M, Pernazza A, Mura F, et al. A pilot multimodal study of cervical cancer: Raman spectroscopy as a molecular fingerprint tool. PLoS One 2026;21:e0327286.
23. Sheng B, Pan S, Ye M, Liu H, Zhang J, Zhao B, et al. Single-cell RNA sequencing of cervical exfoliated cells reveals potential biomarkers and cellular pathogenesis in cervical carcinogenesis. Cell Death Dis 2024;15:130.
24. Zhang W, Cao Y, Ma W, Xu J, Bao Z, Yan J, et al. Application of optical coherence tomography in the evaluation of cervical lesions: a multicenter study. Chan ke za zhi 2024;59:299–306.
25. Cui X, Yang D, Zhang J, Zhao Y, Cui Z, Wang C, et al. Clinical value of optical coherence tomography in the early diagnosis of cervical cancer and precancerous lesions: a cross-sectional study. Front Oncol 2024;14:1423128.
26. Chen K, Wang Q, Ma Y. Cervical optical coherence tomography image classification based on contrastive self-supervised texture learning. Med Phys 2022;49:3638–53.
27. Zuo X, Liu J, Hu M, He Y, Hong L. A deep learning model for cervical optical coherence tomography image classification. Diagnostics (Basel) 2024;14:2009.
28. Han T, Qian S, Meng J, Zhou L, Xi G, Yang L, et al. Detection of human cervical cancer by probe-based quantitative optical coherence tomography. Laser Photonics Rev 2025;19:2401479.
29. Paczos T, Bonham A, Canavesi C, Rolland JP, O'Connell R. Near-histologic resolution images of cervical dysplasia obtained with gabor domain optical coherence microscopy. J Low Genit Tract Dis 2021;25:137–41.
30. Zhang W, Fine JL, Pei X, Cao Y, Liu Y, Yan J, et al. Characteristics and utility of high-resolution optical coherence microscopy images of endocervical canal lesions. Am J Clin Pathol 2024;162:392–400.
31. Malone J, Lam S, Buenconsejo A, Hohert G, Miller DM, Proctor L, et al. Endoscopic optical coherence tomography (OCT) and autofluorescence imaging (AFI) of the endocervical canal for cervical cancer screening. Proc SPIE 2022.
32. McLean JP, Fang S, Myers KM, Hendon CP. Human cervix imaging and analysis with optical coherence tomography. Proc SPIE Biophotonics Congress 2021:jw1a.15

Turk J Oncol 2026;41(4):359–370
doi: 10.5505/tjo.2026.65934

33. Brenes D, Salcedo MP, Coole JB, Maker Y, Kortum A, Schwarz RA, et al. Multiscale optical imaging fusion for cervical precancer diagnosis: integrating widefield colposcopy and high-resolution endomicroscopy. IEEE Trans Biomed Eng 2024;71:2547–56.
34. Ali H, Sheikh A, Saleem N, Naqvi W, Ali A. The role of artificial intelligence in cervical cancer screening: from Pap smears to deep learning. Innovapath 2025;1:1–13.
35. Wilson A, Cropper A, Ma Y, Adams EJ, Mehew S, Morgan M, et al. Improving laboratory workforce efficiency using AI-assisted digital cytology within an HPV-based cervical screening programme: a model-based evaluation for the NHS Cervical Screening Programmes. BMJ Open 2026;16:e113298.
36. Yang W, Jin X, Huang L, Jiang S, Xu J, Fu Y, et al. Clinical evaluation of an artificial intelligence-assisted cytological system among screening strategies for a cervical cancer high-risk population. BMC Cancer 2024;24:776.
37. Chiappa V, Caia C, Interlenghi M, Paolini B, Palladino S, Costeniero D, et al. Development and temporal validation of a proof-of-concept artificial intelligence model for binary classification of cervical cotest. Eur J Cancer Prev 2026.
38. Ahmed SR, Befano B, Lemay A, Egemen D, Rodriguez AC, Angara S, et al. Reproducible and clinically translatable deep neural networks for cervical screening. Sci Rep 2023;13:21772.