

A Review of High-risk Human Papillomavirus (HPV) Detection Using Deep Learning and Machine Learning

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Abstract

Human papillomavirus (HPV) is one of the most critical viruses that integrates with human cells, and may cause various types of cancer, including cervical and oropharyngeal cancer. It encompasses a wide range of genotypes that vary in their severity and pathogenicity, which are classified as low-risk that often associated with benign lesions such as warts. The high-risk types, which are strongly linked to the development of several cancers, most notably cervical cancer and the head and neck cancer. Epidemiological studies indicate that HPV infection is widespread; yet, most infections are transient and cleared by the immune system. However, in a limited percentage of cases, the infection persists, thereby increasing the risk of malignancy. Early detection and accurate diagnosis are crucial in reducing the burden of disease. Therefore, multiple techniques are employed, including molecular tests such as PCR, immunological markers such as p16, and traditional histological examination using hematoxylin and eosin (Hematoxylin and Eosin) staining. Artificial intelligence (AI) techniques, have emerged as promising tools by utilizing DNA data or analyzing cell images from Pap smears and histopathological images; however, challenges remain regarding the generalizability, interpretation, and integration of these models into clinical practice. This research provides a comprehensive summary of all the studies and methodologies employed in this field that utilize deep learning and machine learning techniques. HPV represents a global health challenge that requires integrated efforts encompassing prevention, such as vaccination, early detection, and treatment, along with leveraging modern technologies to enhance detection accuracy and improve patient outcomes.

Keywords: Cervical Cancer, High-risk HPV, Histopathology, Human Papillomavirus (HPV), Oropharyngeal Cancer.

Introduction

Human papillomavirus (HPV) is a double-stranded DNA virus responsible for a significant proportion of cervical and oropharyngeal-cancers worldwide (1). HPV represents a major global health concern and it's categorized as one of the most common sexually transmitted viral infections worldwide (1, 2). Persistent infection with high-risk HPV types is strongly associated with cervical carcinogenesis and also contributes to other anogenital malignancies including anal, vulvar, vaginal, and penile cancers. Its oncogenic impact further extends to head-and-neck cancers and in particular the oropharyngeal cancer, demonstrating the broad epidemiological importance of HPV-associated disease across different anatomical sites (1, 2). The flowchart for HPV status prediction is explained in Figure 1, where all phases of the prediction stages are illustrated. Cervical cancer screening commonly relies on HPV-based testing, cytology-based

examination, or a combination of both approaches. HPV-based screening detects high-risk HPV infections related to the cervical precancer and cancer development, whereas cytology evaluates cervical cells for morphological abnormalities. Co-testing combines HPV testing with cytology to provide complementary molecular and cellular information and may be applied according to the adopted screening guidelines and patient characteristics (1). These screening strategies support the early identification of women at increased risk of developing HPV-associated cervical lesions (1, 2). However, these methods can be labor-intensive, costly, and limited by inter-laboratory variability (2). The enhanced access to large-scale genomics and imagery datasets has facilitated the development of automated diagnostic models using machine learning (ML) and deep learning (DL) techniques (3). Deep learning techniques have shown great promise for

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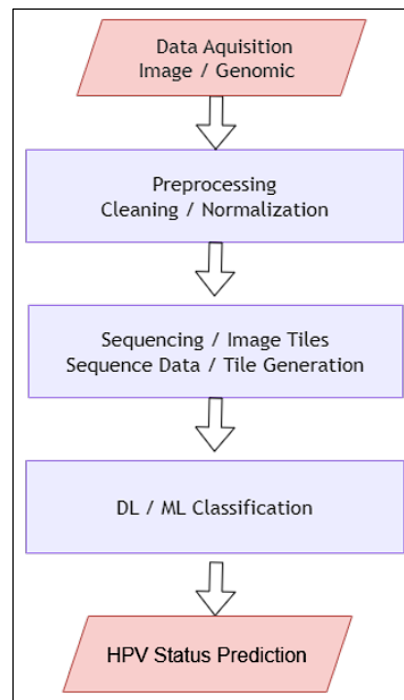


Figure 1: Flowchart for HPV Prediction Phases

use in medical diagnostics by automatically identifying and extracting clinically relevant high-dimensional features from considerably complex biological data (4). Specifically, in the field of research related to HPV, DL techniques have been utilized on a variety of data types such as next-generation sequencing (NGS) data (5). Histopathology images, radiomic imaging datasets, and a microarray data to enhance the accuracy and reproducibility of HPV detection (6). The CNN model used to determine HPV genotypes from NGS reads while deep learning algorithms, trained on standard histology slides have been utilized for the prediction of HPV infection in head and neck cancers (7). Also, recent studies went beyond detection to use DL to explore the prediction of HPV-DNA integration sites (3, 8, 9), the prediction of its oncogenic potential and the dynamics of the viral-host interaction (9). These studies establish a foundation for comprehensive systems that combine detection at the molecular level and provide personalized treatment options. Emerging frameworks combining genomics, cytology, and clinical data are moving toward an integrated AI-assisted diagnostic and therapeutic pipeline. Therefore, this review aims to examine recent advances in deep learning and machine learning-based methods based for HPV detection by emphasizing high-risk genotypes and to discuss how these advances can contribute to the

development of intelligent treatment recommendation systems for HPV-associated diseases.

Cancers Caused by High-risk HPV

High-risk human papillomavirus (HPV) infection basically can cause a variety of epithelial malignancies worldwide (10). Therefore, epidemiological studies estimate that HPV contributes to approximately 630000 new cancer cases annually which represent about 5 % of all cancers worldwide (10). These genotypes are responsible for nearly 70% of cervical cancers and a substantial fraction of oropharyngeal and other different types of squamous cell carcinomas (11). The causal link between persistent HPV infection and carcinogenesis has been extensively validated through both molecular and population studies (9). Cervical cancer remains the most prevalent malignancy directly associated with high-risk HPV infection in particularly the low and middle-income countries where screening coverage is limited (12, 13), however, the HPV has been further investigated in oropharyngeal cancer (14). On the other hand, different stage of cancerous have been examined with a various tissue infection (15). Persistent infection with high-risk HPV genotypes initiates a cascade of molecular alterations that transform normal epithelial cells into neoplastic lesions (16). This transformation is caused by the integration of viral DNA into the host genome disrupts E2 gene regulation leading to

overexpression of the E6 and E7 oncoproteins, which inactivate the p53 and retinoblastoma (Rb) tumor-suppressor pathways (17, 18). This genomic disruption leads to excessive cell division, genomic instability, and eventually cancerous transformation (19).

Morphologically, the impacted cervical epithelial cells exhibit koilocytosis, nuclear enlargement, and hyperchromasia which are considered hallmark diagnostic features in Pap smears and histopathological evaluations (7, 9). Highly sophisticated deep learning systems are able to detect some of the minute cytological details to improve their diagnostic capabilities over direct cytological methods. Advanced deep learning systems are able to detect some of the subtle cytological patterns to improve their diagnostic capabilities over direct cytological methods. Some studies conducted a CNN-based frameworks for the detection of precancerous lesions from cytology and colposcopy images with a diagnostic accuracy of over 90%, which has highlighted the essential role of intelligent systems in early diagnostic screening (15, 20, 21). Other studies developed a healthcare Micro-holography system based on deep learning to detect unusual cervical cells at the precancerous stage, presenting a cost-effective and scalable solution for economically challenged healthcare systems (22). Collectively, these studies highlight the usefulness of intelligent systems to detect high-risk HPV and the associated morphological alterations at an early stage.

From another perspective, HPV is integral for the pathogenesis of Head and Neck Squamous Cell Carcinomas (HNSCCs), especially Oropharyngeal Squamous Cell Carcinomas (OPSCCs) (23). High-risk HPV in OPSCCs typically arise from the epithelium of the tonsillar crypts and have a rather unique molecular profile that is characterized by p16 over-expression (24), fewer genomic mutations and better prognosis to radiation and chemotherapy (2). The CT images also provide a promising basis for HPV status prediction, although relatively poor predictive accuracy has been reported using a CNN-based model with Gradient-weighted Class Activation Mapping (Grad-CAM) employed for model interpretation (25). Radiomics and Positron Emission Tomography (PET) adopted as imaging techniques for HPV status prediction in OPSCC and found that HPV-positive tumors have unique metabolic and

texture-based imaging features (26, 27). Another study has developed an explainable machine-learning approach using pretreatment clinical data to predict HPV status in patients with OPSCC (28). From this perspective it can be concluded that the biological foundation for applying the deep learning models in digital HPV detection from radiological images and shows that deep learning is able to depict viral-oncogenic patterns across different imaging techniques. Apart from head and neck cancers the infection with high risk-HPV is associated with anal, vulvar, vaginal and penile carcinomas which involve processes of viral integration and oncoprotein expression (11). Analyzed a molecular panel for HPV genotyping by using a machine learning in an Asian cohort and observed a diverse range of high-risk HPV profiles (12). This is vital epidemiological data for the region's vaccine implementation and screening processes.

Image based methods and developments in molecular diagnostics improve the understanding of the cells and genomic effects of high-risk HPV infection. Another research utilized high resolution microscopy with deep learning approaches for HPV detection, thereby uncovering structural alterations on a nanoscale level, the proposed findings support the ties between viral activity and disruption of cellular microstructures (29). Furthermore, molecular modeling studies has shown deep learning's capability on the prediction of the oncogenic potential for various HPV strains, thereby connecting biological molecule patterns with computational prediction (19).

High-risk HPV associated cancers are malignancies caused by any type HPV strain that are distinct in tissue-specific expressions and their clinical consequences. Accurate identification of high-risk HPV infections would be helpful in early intervention, targeted treatment and reduced cancer mortality solidifying the biomedical foundation for the deep-learning approaches.

Data Sources and Modalities for HPV Detection

The effectiveness of deep-learning models for HPV detection depends largely on the type and quality of input data. Different studies have used diverse biomedical data sources such as genomic sequences, histopathology slides, and radiological images to identify and classify HPV infections (22).

An illustration of available datasets for the HPV detection is shown in Table 1, each data type provides unique information that supports the detection of high-risk HPV infections and the prediction of their clinical outcomes.

DNA and Genomic Dataset

DNA-sequence data form the foundation for most molecular HPV detection systems. Next-generation sequencing (NGS) technologies enable researchers to analyze the entire HPV genome with high accuracy.

- a) **PaVE:** It aligned reads to an HPV reference sequence downloaded from PaVE to assemble complete HPV genomes and study integration (30).
- b) **VISDB (Viral Integration Site Database) :** Databases of virus integration sites in the human genome, including HPV, VISDB collects around 77000 integration sites across multiple oncogenic DNA viruses and retroviruses (31).
- c) **VIS Atlas:** A database with an “atlas” of integration breakpoints for HPV, HBV and EBV (3).

A HPV-KITE developed as an automated sequence-analysis software for rapid genotype detection (9). On the other hand, works such as DeepHPV (17), VISDB (31), DeepVISP (32) used deep learning architectures to predict HPV integration sites within human DNA. These studies have shown that deep learning models trained on nucleotide sequences can successfully classify HPV types by locating viral integration events and predict oncogenic potential and clinical outcomes (19).

Histopathology and Microscopy Images Datasets

Microscopy and histopathological images are valuable resources for detecting HPV. Deep learning, specifically convolutional neural networks (CNNs), can identify changes in cellular and tissue structure that are associated with HPV infection. Publicly available cervical cytology datasets, such as BiCervi (33) and CPSMI2025 (34), provide microscopy images representing different cervical cell abnormalities for developing and evaluating AI-based screening models. Although these datasets do not directly provide HPV-status labels, they support the analysis of cytological

abnormalities associated with HPV-related cervical disease.

A deep-learning model has been developed to identify HPV infection in head-and-neck cancer-tissue images and proved that automated histopathology analyses can achieve similar outcomes to expert pathologists (11).

- a) **BiCervi Dataset (Pap Smear Images):** Microscopic Pap smear images composed of 3,000 cervical cytology images, classified into eight diagnostic categories including normal, precancerous, and malignant cervical abnormalities (33).
- b) **CPSMI2025 Dataset (Pap Smear Cells):** The dataset contains 2,169 Pap smear images across nine cytological categories (34).
- c) **TCGA-CESC (Cervical squamous cell carcinoma) and TCGA-HNSC (head and neck squamous carcinoma):** These datasets were used with TCGA slides to classify cervical cancer from images (35).
- d) **TCIA-Head-Neck 500 (HNSCC):** imaging dataset for HPV-positive vs HPV-negative classification (36).
- e) **S-BIAD1168:** Histopathology (WSI) in isyntax format for a multiclass cervical cancer whole-slide images with HPV status (20).

Microscopic-image studies applied deep learning to high-resolution microscopy to distinguish HPV presence at the subcellular level (29). On the other hand, medical-imaging and radiomics data provide non-invasive alternatives for predicting HPV status. Machine learning models have been applied to computed-tomography (CT), magnetic-resonance imaging (MRI), and positron-emission-tomography (PET) scans. A recent study compared 2D and 3D CT-based segmentation techniques for HPV prediction in oropharyngeal cancers (22), another study have used PET imaging with deep learning to discriminate HPV-positive from HPV-negative tumors (26). The CNNs could extract radiomic features related to HPV infection (23), however, similar findings has been revealed by using MRI data (26). These studies collectively indicate that imaging biomarkers derived from deep learning models can complement molecular testing in assessing HPV related cancers.

Table 1: Available Dataset for HPV

Dataset Name	Data Type	Contents / Description	References
PaVE	DNA / Genomic Data	Repository of complete HPV genomes, reference sequences, and curated genomic information.	(30)
VISDB	Viral Integration Sites	77,000 experimentally validated viral–host integration sites for HPV, HBV, EBV, and others.	(31)
VIS Atlas	Viral Integration Sites	Comprehensive atlas of integration breakpoints for HPV, HBV, and EBV.	(3)
BiCervi Dataset	Microscopy (Pap Smear) Images	3,000 Pap smear images across 8 classes	(33)
CPSMI2025	Microscopy (Pap Smear) Images	2,169 Pap smear images for nine cytological categories	(34)
TCGA-CESC	Histopathology (WSI) and Genomic	Cervical cancer whole-slide images and molecular data.	(35)
TCGA-HNSC	Histopathology (WSI) and Genomic	Head and neck cancer slides with HPV annotations and clinical data.	(35)
TCIA Head-Neck 500	Radiology (CT) Imaging	CT scan dataset containing HPV-positive and HPV-negative tumor cases.	(36)
S-BIAD1168	Histopathology (WSI) in Isyntax format	Cervical cancer whole-slide images with HPV status	(20)

Multi-modal and Integrated Data Approaches

Current studies increasingly focus on integrating multiple data types to improve predictive performance. Recent study discuss using the machine learning to interpret the extended HPV genotyping results in screened clinical populations (12). Another approach proposed a multimodal deep learning framework that integrating colposcopy, cytology and HPV test results for improved diagnostic performance in cervical screening (37). Another attempt developed predictive models that included viral genotype data within more extensive diagnostic systems for cervical cancer (38). These multimodal approaches have shown promise for more complex clinical systems in the future that provide intelligent clinical decision support.

Deep Learning Architectures

The design of deep learning systems to detect HPV has utilized various model architectures to extract features from radiologic, histopathologic, and genomic data, varying in complexity and usage, yet sharing the goal of automating the extraction of features and improving diagnosis accuracy (9, 12). Recent studies have shown that such approaches can outperform the techniques in traditional diagnostics, as they have been able to detect data patterns that cannot be detected through manual analysis (8).

Convolutional Neural Networks (CNNs)

Convolutional neural networks (CNNs) are among the most frequently adopted deep learning architecture in HPV detection studies due to their effectiveness in learning complex patterns in image and sequence-based data modalities. CNNs simplify the complexity of data by reducing the number of required complex features and enhancing the performance of a designated model (8). A CNN also used to detect the presence of HPV in head and neck squamous cell carcinoma (HNSCC) by the classification of histopathological slides (11). The model was based on the use of Hematoxylin and eosin (H & E) stained datasets obtained from The Cancer Genome Atlas (TCGA). Their CNN utilized multiple convolutional layers followed by Rectified Linear Unit (ReLU) activation and pooling to capture structural differences between HPV-positive and HPV-negative tissues. The work realized that CNNs could capture morphological markers such as keratinization and tumor architecture that are associated with HPV-driven oncogenic changes.

Although many institutions contributed to the data collection, there were only 48 OPSCC patients in the TCGA cohort, compared to many non-OPSCC head and neck tumors, this class imbalance in the dataset reduced the model's ability to generalize features specific to HPV-related OPSCC. In reference to the model's robustness, the study suggested the use of non-OPSCC samples, while highlighting the need of larger OPSCC-focused

cohorts to ensure balanced training and reliable evaluation across clinically relevant subtypes (11). In the analysis of genomic sequences, various CNN-based models have been introduced to detect viral DNA integration and oncogenic patterns, the DeepHPV model developed by employing a one-dimensional CNN architecture with convolutional and pooling layers to identify HPV-host integration sites from next-generation sequencing (NGS) reads. By encoding DNA sequences into one-hot-encoded matrices, the model was able to capture local motifs and positional dependencies within the nucleotide context (17). Similarly, DeepVISP, enhanced the detection of sequence motifs by combining CNN-based feature extraction with pattern visualization for more precise short sequence motifs that influence viral-integration preferences (32). More recently, the GenoMoE framework advanced sequence-based HPV integration-site prediction by combining the pretrained DNABERT-2 model with a multi-level Mixture-of-Experts architecture, the model evaluated on the dsVIS and VISDB datasets (39).

Despite their success, the CNN models for genomic analysis encounter number of limitations, the first one is its dependence on extensive labeled data which is a major constraint as HPV-integration site annotations that are limited and costly to obtain (8). More recent works, explored deep neural networks for cytology-based HPV detection, confirming that digital pathology can effectively support automated diagnosis (40). Another study suggested a CNN-SVM hybrid framework for the classification of cervical cytology images using the Herlev and SIPaKMeD datasets. The CNN module built on the LeNet architecture which served as a feature extractor to generate deep spatial features of cervical cell images while a Support Vector Machine (SVM) was then used as the model's classifier. The proposed framework attained a high diagnostic accuracy of 99.3 % exceeding the performance of individual CNNs and manually engineered feature approaches with respect to computational efficiency and the LeNet model's depth. Moreover, the model required significant levels of preprocessing and normalization and its generalizability to external datasets remains unverified due to the nature of the training data (41).

At last while the CNNs perform well in task-specific training but their generalizability across

datasets such as TCGA, GenBank and the independent clinical data remains less explored which impact clinical translation (32).

Generally, the CNN models have contributed substantially in HPV-detection research by facilitating accurate classification and discovery of hidden morphological and genomic biomarkers. However, to achieve model transparency as well as ensuring dataset diversity and validation using data from multiple clinical centers remains essential for transitioning CNN models from research settings into practical diagnostic workflows.

Hybrid and Feature-enhanced Models

Hybrid models combine both deep learning and traditional machine learning or integrating handcrafted features extraction methods to increase the interpretability and ensure model stability with robustness in HPV-detection tasks, such strategies attempt to mitigate challenges associated with purely deep learning models by embedding explicit features that reflect biological structures or domain-specific knowledge.

In feature-Enhanced Models, the FLock model has utilized graph-based modeling to handle spatial interactions among cells in histopathology images where each nucleus was represented as a node and edges capturing morphological and topological relationships. The resulting graph descriptors provided biologically meaningful representations correlating with HPV infection status and tumor prognosis, this method offered improved interpretability because it visualized intercellular architecture rather than depending only on convolutional activations. The model requires accurate nucleus segmentation and involves considerable computational demands, which potentially constraining scalability for whole-slide-image analysis (14).

Another feature-based approach investigated HPV-associated morphology by extracting quantitative morphometric and colorimetric characteristics directly from individual tumor cells in H&E-stained oropharyngeal squamous cell carcinoma tissues. A set of 41 cellular features was used with a Random Forest classifier to predict HPV positivity, achieving approximately 90% classification accuracy. Feature-importance analysis additionally provided information about the cellular characteristics contributing to HPV prediction. Such feature-driven approaches

improve explainability by connecting predictions to measurable histomorphological properties; however, their performance remains dependent on reliable cell identification and feature extraction (42). More recently, a study developed a weakly supervised approach for predicting HPV status from H&E-stained whole-slide images of oropharyngeal squamous cell carcinoma. The approach employed the Clustering-constrained Attention Multiple-Instance Learning (CLAM) framework for slide-level HPV prediction and complemented the deep-learning analysis with cell-level morphological assessment of high-attention regions. Morphological features were extracted from segmented cells and analyzed using a Random Forest classifier, which achieved approximately 83% cell-level classification accuracy. The analysis demonstrated that nuclear and staining-related characteristics, particularly hematoxylin optical-density features, contributed substantially to distinguishing HPV-associated morphology. This combination of attention-based deep learning and conventional morphometric analysis provides additional biological interpretation of the patterns learned by the model (43). Recent study discussed an attention-based network for detecting HPV in histological slides of oropharyngeal carcinoma, this framework integrated handcrafted features of nuclear

morphology parameters such as size, shape, and texture with deep feature maps extracted by a residual convolutional backbone. Attention module utilized to focus on important patterns related to diagnostical regions improving both accuracy and model transparency, this study underlines the demonstration of how attention mechanisms improve interpretability in digital pathology. On the other hand, the method depended on extensive, high-quality annotated slides and GPU-intensive training and that make it difficult to deploy in routine clinical workflows (44). Hybrid and feature-enhanced approaches share the objective of extending conventional deep learning beyond representations learned directly from image pixels. However, they differ in how this enhancement is achieved. Hybrid models explicitly integrate deep representations with handcrafted features or conventional machine-learning components, whereas feature-enhanced models enrich the representation through additional structural, spatial, morphological, or biologically informed information. Accordingly, both categories are discussed within the same broader AI framework while being distinguished according to their methodological characteristics. Table 2 summarizes representative approaches, their incorporated features, interpretability advantages, and principal limitations.

Table 2: Hybrid and Features Enhanced Approaches

Category	Main Method	Features Used	Main Advantage	Limitation	References
Feature-enhanced	Cell-graph modeling	Nuclear and spatial features	Captures cellular organization	Requires nucleus segmentation	(14)
	Random Forest	41 morphometric and colorimetric features	High interpretability	Depends on cell segmentation	(42)
Hybrid	CLAM + Random Forest analysis	Deep and cellular morphological features	Links attention regions with cellular morphology	Relatively small WSI cohort	(43)
Hybrid	Attention DL + ML	Morphological features	Combines deep and handcrafted information	Requires annotated images	(44)

Transfer Learning Models

Transfer learning is widely recognized as an essential approach to overcome the limited availability of large and annotated medical datasets in HPV detection (36). Instead training deep learning architectures from scratch, the authors employ fine-tuning of pretrained CNNs that have already learned generic image representations from large-scale datasets such as

ImageNet (45). This strategy enables models to reuse low-level visual features such as textural, structural, and edge-based features while adapting high-level representations to domain-specific medical or cytological characteristics, such a strategy has demonstrated significant effectiveness in cytology and histopathology where the collection of extensive labeled data is both requires significant time and resources.

Recent HPV-focused studies have shown that transfer learning enhances model generalization and interpretability thereby supporting improved diagnostic integration in real-world settings (46). Another study applied transfer learning using ResNet-50 and ResNet-101 architectures to improve HPV detection from cytological images, their dataset consisted of digitized Pap smear images in which transfer learning significantly increased predictive performance compared with networks trained from scratch. The models were further optimized through fine-tuning on the cervical-cytology dataset enabling the extraction of discriminative morphological features associated with HPV infection. The approach achieved 94.8 % accuracy which demonstrating that pretrained feature extractors can generalize effectively even with limited labeled data (36).

Transfer learning is adopted in radiomic analysis to extract biomarkers from CT and MRI scans of oropharyngeal cancer patients aiming to assess HPV status without medical intervention utilized in features extraction from image by deep neural model. By modifying the CNN, the authors attained improved classification across multiple patient cohorts and achieved an AUC of 0.81. However, this study highlights the challenges of heterogeneity in radiomic features such as variations in imaging conditions as well as the patient demographics which may impact model reliability (23).

Transfer learning offers a robust framework for knowledge transfer from large generic datasets to specialized HPV image tasks and that accelerates convergence and also reduces dependency on large datasets but its success depends on the similarity between source and target domains as well as carefully optimized hyperparameters to prevent catastrophic forgetting of learned features.

Model Evaluation and Performance Comparison

The performance recorded by the deep learning (DL) and machine learning (ML) adopted in HPV detection and cancer risk assessment shows a considerable variation depends on whether the system use image or genomic data sources. For instance, high predictive ability recorded for HPV related lesions based on MRI, CT, and PET imaging using the deep learning algorithms have shown acceptable assessment between HPV-positive and HPV-negative oropharyngeal cancers with

sensitivity and specificity values often exceeding 85% accuracy in validation cohorts, however, this score should be more reliable in medical applications (6, 23, 26, 44). Deep learning models for Radiomic utilized multiparametric MRI or FDG-PET achieved reliable non-invasive prediction of HPV status by leveraging texture patterns as an indicative of viral oncogenesis (6, 22, 26). A non-invasive CT radiomics-based machine-learning approach using radiomic feature selection and a Random Forest classifier to predict HPV status in oropharyngeal cancer, achieving 91% test accuracy and 77% AUC (27).

In contrast, genomic models that emphasizes sequence data and integration sites or the viral-host genomic interactions such as the genotype-level ML classifiers as implemented in HPV-KITE and ExplaiNN has enabled efficient identification and lineage interpretation with explainability and scalability (9, 47). Furthermore, NGS-based HPV genotyping studies validated the robustness of these computational tools for both mono and co-infections (5, 48). The application of genomic embeddings and neural architectures also enables the detection of high-risk genotypes and prediction of their oncogenic potential with high accuracy, however, this approach relies heavily on the availability of genomic sequence data (9).

A comparison of these methodologies shows that the image-based approaches tend to offer intuitive clinical visualization and diagnostic interpretability while genomic-based models provide high molecular precision and subtype-level resolution. Integrated strategies that fuse imaging and omics information such as the cross-modal deep learning model that combines the cytology, and HPV tests represent a promising convergence (37). Recent multimodal deep learning frameworks have demonstrated enhanced classification performance for cervical cancer, achieving high AUC values and strong generalization performance (20, 49). Past studies further demonstrated the benefit of multimodal integration by combining colposcopy images, cytology, and HPV testing. Their cross-modal model achieved an AUC of 0.921, outperforming cytology alone [0.749], HPV testing alone [0.742], and the multi-image colposcopy model [0.845], indicating that complementary evidence from different modalities can improve screening performance (37).

Recent studies showed that deep learning models achieved strong performance in identifying HPV-related cervical cancer patterns from whole-slide images as an effective approach for cervical cancer subtyping (50). While another study improved diagnostic support for HPV-associated and non-HPV-associated adenocarcinoma using EdgeNeXt-SEDP (51). On the other hand, an interpretable framework that enhanced understanding of HPV-related morphological features and thus improved the model transparency (52). A brief illustration of

deep learning models and their performance illustrated in Table 3.

Overall, genomic models may achieve superior performance compared to image systems in genotype-level discrimination and mechanistic insight while the image-based models remain superior for real-time clinical screening and spatial localization. The integration of these modalities is likely to deliver highly robust and comprehensive diagnostic models for HPV-associated malignancies.

Table 3: Deep Learning Models and Their Performance

Model Type	Data Type	Key Features	Reported Performance Metrics	References
CNN	Histology Images	Convolutional network for tissue-level HPV prediction	AUC: 83.0% AP:93.0%	(11)
CNN-SVM Hybrid	Cytology Images	Combines CNN features with SVM for classification	Accuracy: 99.3%, sensitivity: 98.9%, specificity: 99.4%	(41)
Attention Residual Network	Histology Images	Attention layers for interpretability and regional focus	Accuracy: 91%	(44)
CNN	Microscopy Images	High-resolution image analysis via deep CNNs	Sensitivity: 83.6%, specificity: 83.33%	(29)
Graph Neural Network (Flock)	Histology Images	Models cell graphs and spatial dependencies	AUC: 84.0% AlexNet: 78.0% ResNet:81.0%	(14)
DeepHPV (CNN)	DNA Sequence	1D CNN for HPV-host integration site detection	AUROC: 72.0%	(17)
DeepVISP (CNN)	DNA Sequence	Combines CNN with motif pattern recognition	AUC: 81.1%	(32)
CNN (Radiomics)	CT/MRI Scans	CNN-based extraction of radiomic signatures	AUC: 81.0%	(23)
ML Classifier (Radiomics)	MRI	Multiparametric radiomic feature-based classification	Logistic Regression AUC: 77.0% Random Forest AUC: 76.0% XGBoost AUC: 0.71	(6)
CNN (Transfer Learning)	Cytology Images	Fine-tuned ResNet model on small dataset	ACC Herlev: 98.3%, ACC SIPaKMeD : 97.5%	(36)
Cross-Modal Deep Learning	Multi-modal (Colposcopy + Cytology + HPV Tests)	Integrates multiple modalities for screening	AUC: 0.921 (cross-modal); 84.5% (multiple-image); 83.7% (cytology + HPV)	(37)
CNN + Machine Learning (Hybrid WSI Framework)	Histology Images (WSIs) SCC + AC classes	Cervical Cancer Subtyping	Patch-level AUC: 96.0%; WSI-level AUC: 96.4%	(50)
EdgeNeXt-SEDP (Lightweight CNN + Decision Support Framework)	Histology Images (WSIs, Cervical Adenocarcinoma – HPVA vs NHPVA)	Image Patterns	Accuracy: 97.63%; Precision: 97.61%; Specificity: 96.98%; Macro-F1: 97.58%	(51)

Clinical Relevance and Real-world Performance

The adoption of artificial intelligence for HPV detection models is confirmed not only by accuracy but also scalability and interpretability as well as the cost effectiveness in real-world workflows where the image systems have developed toward clinical validation particularly for cytology and histopathology applications.

The reliability of AI-based cervical screening has also been investigated in relation to expert-dependent interpretation. A recent study developed a deep-learning system for automated p16/Ki-67 dual-stain cytology and evaluated its performance against manual dual-stain assessment and conventional cytology. The automated approach demonstrated comparable sensitivity with improved specificity compared with manual evaluation, highlighting the potential of AI-assisted methods to support more objective and reproducible cervical screening (46).

Automated dual-stain cytology analysis and digital pap-smear classification improved the process efficiency and reproducibility in cervical screening programs (46, 53). For instance, DeepPap is a CNN framework which achieved comparable performance to the specialists in cervical cell classification (53). Though, supervised deep embedding methods enhancement make the diagnostic more reliable across multicenter cohorts (49). Similarly, point-of-care optical microholography systems combined with deep learning techniques enabled low-cost cervical cancer screening in resource-limited settings (54). Genomic models designed using machine learning approaches offered strong translational potential for HPV risk prediction and vaccine surveillance, for example the NGS-based tools including HPV-KITE and ViraMiner provide rapid and accurate genotyping adaptable to be used for monitoring in public health (5, 9, 48). Predicting algorithms designed for the sake of examining the persistence of high-risk HPV after surgical procedures such as conization can support monitoring after operation and personalized care which provide more comfortable and reliable solution for patients (29). Moreover, interpretable neural networks like ExplainNN assist the regulatory acceptance by providing transparent decision logic for classifying HPV genotypes (47).

From a clinical perspective a decision support tools combined within personalized health platforms represents a significant advancement toward HPV prevention and management, a knowledge-graph-based recommender systems have been developed to enhance vaccination adherence and increase risk awareness among populations (55). Furthermore, web-enabled machine learning frameworks can also facilitate continuous monitoring of cervical health. In spite of the presented advancements in this field but real-world adoption remains constrained by data heterogeneity with the limited annotated datasets and challenges in generalizing across diverse populations (12). The continuous benchmarking and external validation across varied patient groups are crucial for regulatory approval and clinical trust along with the interpretable AI offers considerable potential to reshape early detection, prognostication and precision prevention of HPV-associated malignancies.

Challenges and Limitations

There are many obvious limitations in the field of human papillomavirus detection, despite the great progress made in the use of deep learning there is a continuing constraint related to the quality and representation of current datasets. Existing approaches rely heavily on small dataset that are collected at institutions with the lacked diversity in HPV genotypes and patient demographic. The imbalance between high-risk and low-risk HPV or negative samples appeared in most of related dataset could reduce the robustness of classifiers and may leads to overfitting (52), furthermore the genomic sequencing workflows differ across laboratories and this can generate inconsistent annotation standards (9).

Such variability limits generalization and reproducibility of models in particular when the algorithms are implemented across different clinical settings. The black-box nature of deep neural network raises concerns including interpretability and clinical trust while clinicians need transparent reasoning behind predictions in HPV genomics involving viral integration sites or oncogenic potential. Networks such as ExplainNN which have been developed to enhance the explainability, have had limited adoption in HPV studies and remains limited (47). Studies utilizing CNNs for cytology and histopathology rarely include interpretability layers and this leads to

minimize the acceptance by clinicians and regulatory validation (11). Deep models trained on cytology (41), MRI (6), PET (26) tend to perform poorly when applied to various modalities due to differences in data distribution and imaging parameters. Some studies have reported encouraging performance in HPV-status prediction from images when they employ few independent external validation cohorts without standardized protocols for training and testing splits comparing different models which makes the results unreliable (45). This lack limits the transition from research prototypes to clinically approved diagnostic tools (46).

HPV detection models based on artificial intelligence rely on sensitive clinical and genomic data which raising data sharing and privacy challenges (12), most datasets still restricted or not publicly accessible thereby impeding reproducibility and collaborative development. Furthermore, deep learning models trained on regional cohorts may unintentionally encode demographic biases which generate unequal healthcare outcomes (23). The ethical adherence and explainable audit processes considered necessary issue for the patient safety and regulatory approval (55). While deep learning models such as CNNs, LSTMs and hybrid multimodal frameworks require significant computational resources including GPU and large dataset (45), in the low and middle-income regions where HPV burden is high the adopted structure for model training and the deployment is often insufficient (2). Lightweight models proved its superiority and considered desirable for real-time screening (54), but usually trade off interpretability and accuracy (49). In addition, the federated learning approaches and cloud-based framework could mitigate data access restrictions but remain technically and logistically challenging. Despite strong performance CNN models face integration obstacles with the existing clinical workflows and thus pathologists and oncologists may resist automation without transparent validation evidence (46). Finally, the real-world scenarios often involve noisy clinical data which reduce the model reliability because of this continuous collaboration between clinicians and AI systems include retraining with clinician involvement and the post deployment monitoring

are essential to ensure safe adaptation in routine screening programs.

Conclusion

Deep learning enabled new opportunities for detecting and managing high-risk HPV infections, a diverse range of data modalities such as imaging, genomics and cytology have been used and DL systems can classify HPV genotypes and assess cancer risk with high accuracy. These technologies have the potential to facilitate early diagnosis which improves treatment planning and reduce the development of HPV-related cancers. However, challenges still exist before these models can be widely adopted in clinical settings. Issues such as the limited availability of data and lack of standardization continue to slow progress. Collaboration among researchers and clinicians is critical to ensure these systems are safe, reliable and fair for all populations.

In the future, integrating artificial intelligence into routine screening and patient care systems could transform HPV prevention and treatment. However, AI-based diagnosis should be considered as one component of a broader HPV prevention and cancer control strategy rather than a substitute for primary prevention. Established preventive measures, particularly HPV vaccination, together with appropriate screening and clinical follow-up, remain essential for reducing the burden of HPV-associated diseases. AI should therefore complement these strategies by supporting screening, diagnosis, risk assessment, and clinical decision-making. As deep learning models become more interpretable and accessible then they will play a key role in enabling faster, more accurate and more personalized healthcare solutions for HPV-associated diseases. Future research should therefore focus on larger and more diverse datasets, standardized data acquisition and evaluation protocols, improved model interpretability, and external validation to establish the generalizability and clinical reliability of AI-based HPV detection systems.

Abbreviations

CNN: Convolutional Neural Network, CT: Computed Tomography, DL: Deep Learning, H&E: Hematoxylin and Eosin, HPV: Human Papillomavirus, ML: Machine Learning, OPSCC: Oropharyngeal Squamous Cell Carcinoma.

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Author Contributions

All the authors contributed equally.

Conflict of Interest

The authors declare that there is no conflict of interest.

Data Availability

No new data were generated or analyzed in this review.

Declaration of Artificial Intelligence (AI) Assistance

The authors declare that they did not use AI assisted tools during the writing process. The authors take full responsibility for the content's originality, interpretation and accuracy.

Ethics Approval

Generative AI tools were used solely for general assistance with manuscript structure as well as for language refinement and grammar checking. The authors take full responsibility for the originality, interpretation, and accuracy of the content.

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