International Journal of Health Services
Research and Policy
www.dergipark.org.tr/ijhsrp
IJHSRP

e-ISSN: 2602-3482

Review Article

HARNESSING MACHINE LEARNING IN HPV DIAGNOSTICS: MODEL PERFORMANCE, EXPLAINABILITY, AND CLINICAL INTEGRATION

Bahar ŞENEL

Istanbul University, Istanbul Faculty of Medicine,
Department of Medical Microbiology, Istanbul, Türkiye
Corresponding author: baharkarli@gmail.com

Abstract: *Human Papillomavirus (HPV) remains a significant global health concern, contributing to cervical and oropharyngeal cancers. While traditional diagnostic methods such as PCR-based assays and cytological screenings are widely used, they present limitations in sensitivity, specificity, and scalability. Recent advances in machine learning (ML) have enabled more precise and automated HPV detection and genotyping. This review aims to evaluate the current ML methodologies in HPV diagnostics, compare their performance metrics, and discuss future directions for improving artificial intelligence (AI) -driven HPV screening. CNN-based models exhibited superior performance in cytology and histopathology-based HPV detection, achieving high accuracy in lesion classification. Hybrid models integrating ML with molecular diagnostics improved HPV genotyping precision. Support vector machine (SVM) and random forest (RF) demonstrated efficacy in genomic classification, whereas transformer-based models enhanced feature extraction and risk stratification. Despite these advancements, data heterogeneity, explainability, and clinical validation remain substantial barriers to widespread adoption. ML-driven HPV diagnostics offer unprecedented improvements in efficiency, accuracy, and accessibility. However, critical issues related to data standardization, bias mitigation, and regulatory frameworks must be addressed to ensure clinical reliability. Future research should prioritize explainable AI (XAI), federated learning, and robust validation studies to enhance model generalizability and real-world applicability. The seamless integration of AI-powered tools into HPV screening programs holds transformative potential for early detection, personalized risk assessment, and improved patient outcomes, ultimately contributing to the global reduction of HPV-related malignancies.*

Keywords*: Human Papillomavirus, machine learning, HPV genotyping, artificial intelligence, cervical cancer detection*

Received: February 28, 2025 *Accepted: May 29, 2025*

1. Introduction

HPV is a prevalent sexually transmitted infection, with certain high-risk types being the primary etiological agents of cervical cancer [1]. Traditional diagnostic methods, such as the Papanicolaou (Pap) smear and PCR-based assays, have been instrumental in HPV detection and cervical cancer screening [2]. However, these methods have limitations, including variability in sensitivity and specificity, as well as challenges in scalability and accessibility [3].

HPV infection remains a significant global public health concern. It is estimated that over 80% of sexually active individuals will acquire an HPV infection by the age of 45 [4]. In Turkey, a recently published large-scale study reported a high prevalence of HR-HPV (high risk HPV) (36.3%) among women, with HPV16, 39, and 51 being the most common genotypes. The highest rate (44.1%) was observed in the 17–34 age group [5]. In a large-scale study conducted in Turkey on 94,848 women, it was found that the median age among those who tested positive was 42 and the HPV positivity rate was 3.16%. [6]. In contrast, in the United States, cervical cancer screening programs are evolving to include self-sampling techniques, improving access and early detection [7]. Similar initiatives have been introduced in the United Kingdom, where self-sampling kits are being distributed to increase participation in HPV screening programs [8]. These global differences highlight the need for more accessible, cost-effective, and high-throughput diagnostic approaches.

Recent advances in ML, a subset of artificial intelligence (AI), offer transformative potential in enhancing the accuracy, efficiency, and accessibility of HPV molecular diagnostics [9]. ML techniques, including support vector machines (SVM), random forests (RF), and neural networks, have been successfully applied to classify HPV genotypes with higher precision compared to traditional statistical models. Furthermore, deep learning (DL) architectures, such as convolutional neural networks (CNNs) and transformer-based models, have shown remarkable efficacy in automating the analysis of histopathological and cytological images for HPV-related lesion detection [10].

The integration of ML-driven approaches into microbiological diagnostics enhances pattern recognition, minimizes human error, and improves diagnostic consistency. Additionally, AI-powered solutions facilitate high-throughput screening, enabling rapid and cost-effective HPV genotyping from large datasets [2]. Given the increasing adoption of AI in biomedical research, there is a growing need to evaluate the current advancements, applications, and challenges associated with ML-based HPV diagnostics. This review provides a comprehensive overview of the role of ML in HPV diagnosis and genotyping, highlighting its potential to revolutionize cervical cancer prevention and public health strategies.

2. Machine Learning Approaches in HPV Diagnosis

ML techniques have been increasingly applied in HPV diagnosis to enhance accuracy, reduce human error, and improve the efficiency of screening programs [11]. These approaches leverage vast datasets, including cytological images, genetic sequences, and clinical records, to identify patterns that traditional methods may overlook [10].

2.1. Common Machine Learning Techniques in HPV Diagnosis

Several ML algorithms have been investigated for their potential in HPV diagnosis:

- **SVM:** SVMs have been utilized to classify cervical histopathology images by extracting texture and morphological features, aiding in the early detection of cervical cancer [12,13].
- **RF:** RF models have been applied to predict HPV status from hematoxylin/eosin-stained images, achieving high accuracy in determining HPV positivity in oropharyngeal squamous cell carcinoma [14].
- **k-Nearest Neighbors (k-NN):** This algorithm has been implemented in viral genome classification tasks, demonstrating effectiveness in classifying various viral genomes, including HPV, based on sequence data [15].
- **CNNs:** CNNs have been widely used for automated Pap smear analysis, significantly improving classification accuracy compared to traditional cytological screening methods [16].
- **Recurrent Neural Networks (RNNs):** RNNs have been applied to analyze longitudinal patient data and predict HPV progression trends [17].

- **Hybrid Models (CNN + SVM, CNN + LSTM):** Hybrid DL approaches have been developed to combine CNNs' feature extraction capabilities with SVMs' classification power, yielding superior performance [18].
- **Transformer-Based Models:** Transformer networks, such as Vision Transformers (ViTs), have demonstrated state-of-the-art performance in classifying HPV-associated cervical lesions [19].

2.2. Performance Comparison of ML Models in HPV Diagnosis

Recent advancements in ML have significantly enhanced the accuracy and efficiency of HPV diagnosis. Various studies have employed different ML algorithms to classify HPV status, utilizing diverse data types such as cytological images, genetic sequences, and clinical records. The studies showcase a diverse range of approaches, including CNNs, hybrid architectures, and radiomics-based models, each demonstrating varying degrees of accuracy, sensitivity, and specificity (Table 1).

Table 1. Comparative Performance of DL and Machine Learning Models in HPV Diagnosis and Cervical Cytology Classification

Authors (Reference)	Methods	Results	Sensitivity (%)	Specificity (%)	Accuracy (%)
Yilmaz et al. [20]	XGBoost, CNN	XGBoost achieved 85% accuracy, while CNN reached 93%.	85	85	85 (XGBoost), 93 (CNN)
Lang et al. [21]	3DCNN, Transfer Learning	3D CNN achieved an AUC of 0.81 for HPV status prediction	-	-	81 (AUC)
Ma et al. [22]	CNN + SVM	CNN-SVM combination enhanced feature extraction, leading to better classification accuracy.	86.7	93.5	-
Liu et al. [23]	CNN + Visual Transformer + Multilayer Perceptron (MLP)	Hybrid approach improved classification efficiency, achieving 91.72% accuracy.	-	-	91.72
Ince et al. [24]	SVM, Radiomics	SVM-based model successfully identified carcinogenic HPV types with 95% accuracy.	-	-	95
Sornapudi et al. [25]	VGG-19 CNN	Achieved high accuracy in classifying cervical cells.	-	-	95
Kularathne et al. [26]	CNN	CNN-based model achieved high HPV classification performance.	94	95	96
Zhang et al. [27]	CNN	Model achieved 94.1% accuracy for cervical cell classification.	94.5	93.8	94.1
Rahaman et al. [28]	Hybrid CNN with Deep Feature Fusion	Achieved 99.85% accuracy for binary classification on the SIPAKMED dataset.	99.8	-	99.85

Hybrid DL models (e.g., CNN + SVM, ViTs) consistently exhibit superior classification accuracy, highlighting the potential of multi-modal AI architectures in HPV screening. Radiomics-driven ML models, such as SVM-based radiomics, achieve high accuracy in identifying carcinogenic HPV types, emphasizing their role in precision diagnostics. Traditional ML models like XGBoost and SVM perform well but tend to be outperformed by CNN-based DL models, reinforcing the effectiveness of deep feature extraction in medical image classification.

These findings underscore the transformative role of AI in HPV-related diagnostics, with DL methodologies offering higher accuracy and improved feature representation compared to traditional ML approaches. Future research should focus on integrating multi-modal AI frameworks and leveraging explainable AI (XAI) techniques to enhance clinical interpretability and adoption.

3. Machine Learning for HPV Genotyping

Accurate genotyping of HPV is crucial for determining infection risks, guiding vaccination strategies, and personalizing treatment approaches [29]. Traditional genotyping methods, such as PCR-based assays and hybrid capture, are widely used but have limitations in specificity, sensitivity, and throughput. With the increasing availability of genomic, proteomic, and imaging data, DL models have emerged as powerful tools in HPV genotyping, offering improved accuracy and automation [28].

3.1. Common Machine Learning Techniques in HPV Genotyping

Several ML and DL approaches have been investigated for HPV genotyping:

- **SVM:** SVM models have demonstrated high accuracy in distinguishing high-risk HPV types using genetic sequencing data [30].
- **RF:** RF classifiers have been applied in predicting HPV genotypes based on viral sequence features, improving specificity compared to conventional assays [31].
- **k-NN:** This algorithm has been successfully implemented in HPV subtype classification using molecular signature data [32].
- **XGBoost:** Extreme Gradient Boosting (XGBoost) models have been trained on HPV genomic datasets, outperforming traditional PCR-based methods in classification accuracy [33].
- **CNNs:** CNN-based models have been effective in feature extraction from histopathological slides, improving image-based HPV detection through DL on Pap smear, biopsy samples, and H&E-stained tissue images [34].
- **RNNs:** RNNs have been applied to analyze longitudinal patient data and predict HPV progression trends [35].
- **Transformer-Based Models:** ViTs have demonstrated state-of-the-art performance in classifying HPV-associated cervical lesions [36].
- **Hybrid Models (CNN + SVM, CNN + LSTM):** Hybrid models combining CNNs with SVMs or Long Short-Term Memory networks (LSTMs) have been developed to enhance HPV genotyping accuracy by integrating spatial and temporal features [37].

Conventional machine learning models, such as SVM and RF, have demonstrated high discriminatory performance in detecting HR- HPV genotypes—particularly HPV-16—when trained on well-curated genomic datasets. However, model-specific evidence regarding the accurate identification of HPV-18 remains limited, indicating the necessity for further studies focusing on genotype-level classification performance [31,41].

3.2. Performance Comparison of ML Models in HPV Genotyping

ML models have been extensively applied in HPV genotyping, offering improved accuracy and efficiency compared to conventional molecular techniques. Various approaches, including k-NN, SVM, RF and hybrid DL models, have demonstrated their potential in classifying high-risk HPV types. The table below summarizes the performance metrics of different ML models used for HPV genotyping, highlighting their sensitivity, specificity, and overall accuracy (Table 2).

Table 2. Performance Comparison of Machine Learning Models in HPV Genotyping

Authors (Reference)	Methods	Results	Sensitivity (%)	Specificity (%)	Accuracy (%)
Shakil et al. [38]	k-NN	Achieved 91.62% accuracy using feature selection and explainable AI	99.31	40.91	91.62
Zhai et al. [39]	XGBoost	XGBoost model achieved 81.3% accuracy in predicting high-grade CIN recurrence	81.3	79.2	81.3
Wong et al. [40]	SVM - Linear	SVM-based model classified HPV genotypes with high specificity	56.25	90.91	-
Wong et al. [40]	RF	RF model achieved high specificity for HPV genotyping	53.13	90.91	-
Remita et al. [41]	SVM	SVM-based model successfully identified carcinogenic HPV types with 99.5% accuracy	99.2	99.8	99.5
Remita et al. [41]	RF	RF model reached 99.97% accuracy in HPV classification	99.6	99.99	99.97
Asensio-Puig et al. [31]	RF	RF model achieved high genotyping accuracy	99.5	99.3	99.5
Asensio-Puig et al. [31]	SVM	SVM model provided 98.0% accuracy in HPV lineage classification	98.0	97.8	98.0
Asensio-Puig et al. [31]	k-NN	k-NN model achieved high sensitivity in HPV16 lineage classification	98.0	97.9	98.0
Rahaman et al. [28]	Hybrid CNN with Deep Feature Fusion	Achieved 99.85% accuracy for binary classification on the SIPAKMED dataset	99.8	-	99.85
Klein et al. [34]	CNN on H&E-stained images	Achieved 92.0% accuracy in detecting HPV-positive cases	-	-	92.0

Hybrid CNN models (e.g., DeepCervix) exhibit the highest accuracy (99.85%), reinforcing the role of DL in enhancing HPV genotyping precision. R and SVM consistently achieve high accuracy, demonstrating their effectiveness in genomic classification. Traditional ML models like XGBoost and k-NN perform well but show variability in sensitivity and specificity, indicating the need for further optimization and dataset refinement.

These results emphasize the growing importance of AI in HPV diagnostics, paving the way for more robust, scalable, and clinically applicable genotyping models. Future research should explore multi-modal AI integration and federated learning to further improve the reliability of HPV classification algorithms.

4. Future Perspectives and Challenges

Despite significant advancements in AI for HPV diagnosis, several challenges hinder widespread clinical adoption. A primary concern is the need for large, high-quality, and diverse datasets to train robust ML and DL models. Many current studies rely on small or regionally biased datasets, limiting model generalizability. Collaborative efforts to establish global HPV data repositories and implement federated learning frameworks could mitigate this issue. Federated learning allows multiple institutions to collaboratively develop ML algorithms without sharing raw data, thereby preserving patient privacy while enhancing model robustness [42,43]

Another challenge is model interpretability and explainability, which are critical for clinical adoption. Most DL models function as "black boxes," making it difficult for clinicians to understand decision-making processes [44]. XAI models that provide transparent and interpretable outputs could enhance clinician trust and regulatory approval [45].

Algorithmic bias and fairness in AI-driven HPV diagnosis is another pressing issue. Studies have shown that machine learning models can exhibit biases due to imbalanced training data, leading to disparities in diagnostic accuracy across different demographic groups [46]. Ensuring diverse and representative datasets, along with bias-mitigation techniques, is essential to promote equitable healthcare outcomes [47,48].

In addition, data privacy and security remain significant concerns. AI models trained on patient-sensitive information must comply with data protection regulations such as the General Data Protection Regulation (GDPR) and Health Insurance Portability and Accountability Act (HIPAA) to ensure confidentiality [49]. Federated learning, which enables AI training across decentralized institutions without data sharing, has been proposed as a promising solution [50,51].

Lastly, clinical validation and regulatory approval of AI-based HPV diagnostics pose substantial challenges. Despite promising research results, only a limited number of AI models have been validated in real-world clinical settings or received regulatory approval from organizations such as The U.S. Food and Drug Administration (FDA) [48,52].

Implementing DL solutions requires substantial computational resources and technical expertise. Addressing these barriers through investments in infrastructure and training for healthcare professionals is vital for the successful deployment of DL-based HPV genotyping tools [53].

As new data becomes available, DL models must be continuously validated and updated to maintain their accuracy and relevance. Establishing protocols for regular model evaluation and incorporating new findings will help keep the models current and effective [54].

Achieving regulatory approval for DL-based diagnostic tools involves rigorous validation and standardization processes. Collaborating with regulatory bodies to develop clear guidelines and standards will facilitate the integration of these tools into clinical practice [55].

Future research should focus on conducting large-scale, multi-center validation studies to ensure AI models perform reliably across diverse populations and clinical environments.

In summary, while ML and DL present transformative opportunities for HPV diagnosis, overcoming challenges related to data availability, model transparency, fairness, security, and regulatory compliance is critical. Future research should focus on developing scalable, ethical, and clinically validated AI models that can be seamlessly integrated into existing diagnostic workflows to enhance patient care globally.

5. Integration of Machine Learning with Other Technologies for HPV Diagnosis

The integration of ML with advanced diagnostic technologies has significantly enhanced the accuracy and efficiency of HPV detection. By combining ML algorithms with various diagnostic modalities, healthcare professionals can achieve more precise and timely identification of HPV-related conditions, ultimately improving patient outcomes.

One of the most impactful applications of ML in HPV diagnostics is its integration with imaging technologies to improve the detection and classification of cervical lesions. AI-assisted systems employ

DL models to analyze cytological images, differentiating between normal and abnormal cells, thereby enhancing early cervical cancer screening efforts [56].

Incorporating ML with molecular diagnostic methods has also significantly advanced the identification of HPV genotypes and associated biomarkers. For instance, a diagnostic study demonstrated that integrating HPV genotyping into an AI-driven model substantially improved its predictive accuracy for cervical cancer in women with high-risk HPV infections [57]. Additionally, the development of an HPV genotype detection platform utilizing aggregation-induced emission (AIE) and flow-through hybridization technologies has further enhanced the sensitivity and efficiency of molecular diagnostics [58]. These AI-powered approaches facilitate precise HPV genotyping and biomarker identification, improving the overall management of HPV-related conditions.

Furthermore, self-supervised learning approaches have emerged as promising tools to enhance cervical cytology diagnostics, particularly in resource-limited settings. By leveraging unlabeled images from Pap smear tests, these methods improve performance across various diagnostic tasks, making them highly applicable in low-data environments [59].

Another significant advancement is using multiple instances learning frameworks to detect HPV infection in head and neck cancers through routine histological images. These models enable the analysis of tissue samples to predict HPV status, assisting in patient stratification and informed clinical decision-making [60].

Additionally, the fusion of ML with optical coherence microscopy has facilitated the development of computer-aided diagnostic (CAD) systems for cervical tissue analysis. DL models process high-resolution 3D images to accurately classify cervical tissue types, significantly enhancing diagnostic precision [61].

The integration of machine learning with diverse technological platforms has revolutionized HPV diagnostics, offering higher accuracy, efficiency, and accessibility. These AI-driven methodologies not only enhance early detection and classification but also provide scalable and cost-effective solutions for improving global HPV screening programs. As these technologies continue to evolve, their implementation in clinical settings will play a pivotal role in optimizing patient care and advancing cervical cancer prevention strategies.

6. Ethical and Regulatory Challenges in AI-Based HPV Diagnostics

The integration of AI into healthcare, particularly in the diagnosis of HPV, offers significant advancements. However, it also introduces several ethical and regulatory challenges that must be addressed to ensure safe and equitable implementation.

6.1. Data Privacy and Security

AI models require extensive datasets containing sensitive patient information, raising concerns about data privacy and security. Ensuring compliance with regulations such as the GDPR is essential to protect patient confidentiality. Implementing robust data anonymization techniques and security measures is crucial to prevent unauthorized access and data breaches [62].

The GDPR establishes three key principles for AI-driven decision-making: transparency, ensuring individuals are informed about AI decisions and understand their logic; human oversight, requiring human intervention to validate or override automated decisions; and fairness & non-discrimination, mandating that AI systems minimize bias, ensure accuracy, and prevent discriminatory outcomes. These principles enhance accountability, reliability, and ethical AI use, particularly in healthcare applications [63].

The increasing popularity of machine learning approaches and the rising awareness of data protection and data privacy present an opportunity to build truly secure and trustworthy healthcare systems. Regulations such as GDPR and HIPAA present broad guidelines and frameworks, but the implementation can present technical challenges [64].

Addressing these ethical and regulatory challenges is crucial for the successful implementation of AI-based HPV diagnostics, ensuring that technological advancements translate into improved patient outcomes while upholding ethical standards and regulatory compliance.

6.2. Algorithmic Bias and Fairness

The effectiveness of AI systems in healthcare is profoundly influenced by the quality and diversity of their training data. When datasets lack representation or contain biases, AI models can inadvertently perpetuate existing health disparities, disproportionately impacting certain demographic groups. For instance, AI models trained on homogeneous datasets may not generalize well to diverse populations, leading to less accurate predictions for underrepresented groups [65]. This issue is exacerbated when AI systems are developed using data that do not reflect the demographic diversity of the patient population, resulting in unequal outcomes and potentially widening existing health disparities [66]. Addressing these biases is crucial for developing fair and equitable AI-based diagnostic tools that serve all segments of the population effectively. Ensuring diversity in training data and implementing bias detection and mitigation strategies are essential steps toward achieving this goal [67].

6.3. Transparency and Explainability

AI algorithms often function as “black boxes,” rendering their decision-making processes opaque to clinicians and patients. This opacity can hinder trust and impede the adoption of AI-driven tools in clinical settings. Enhancing transparency and explainability is essential to bridge this gap [68]. XAI aims to demystify these complex models, providing clear insights into how decisions are made, thereby fostering confidence among healthcare professionals and patients alike. For instance, integrating XAI into clinical decision support systems can elucidate the rationale behind AI-generated recommendations, enabling clinicians to make informed choices and facilitating patient understanding [69]. Moreover, regulatory frameworks increasingly emphasize the need for transparency in AI applications to ensure ethical and accountable use in healthcare. By prioritizing explainability, AI systems can become more trustworthy, ultimately enhancing their integration into medical practice and improving patient outcomes [70].

6.4. Regulatory Approval and Standards

The integration of AI-based medical diagnostics into clinical practice necessitates stringent evaluation and approval by regulatory authorities to ensure both safety and efficacy. FDA has been proactive in this domain, authorizing numerous AI/ML-enabled medical devices, with a significant concentration in radiology applications. Notably, two-thirds of these radiology devices received marketing authorization between August 2020 and July 2023 [71]. Establishing comprehensive guidelines and standards is imperative to navigate the intricate regulatory landscape surrounding AI in healthcare. Standardization promotes interoperability and compatibility among diverse AI systems, facilitating seamless integration into existing healthcare infrastructures. Moreover, standardized frameworks enhance trust among healthcare professionals and patients, ensuring that AI applications adhere to consistent safety and performance benchmarks [72]. The FDA has recognized the dynamic nature of AI technologies and is adapting its regulatory approaches accordingly. By focusing on the total product lifecycle of AI tools, the FDA aims to balance patient safety with the promotion of innovation in healthcare. This adaptive regulatory stance is crucial for accommodating the rapid evolution inherent in AI applications [73].

In summary, the successful deployment of AI-based medical diagnostics hinges on rigorous regulatory oversight and the establishment of clear, standardized guidelines. Such measures are essential for ensuring that these advanced technologies are both safe and effective, thereby fostering their integration into routine clinical practice.

6.5. Clinical Responsibility and Legal Implications

AI in medical diagnostics introduces complex questions regarding clinical responsibility and legal liability, particularly in instances of misdiagnosis or errors. Establishing clear delineations of accountability between healthcare providers and AI developers is paramount to navigate potential legal challenges and uphold patient safety.

In scenarios where AI systems function autonomously, it is advocated that developers assume liability for any resultant harm, provided the technology is utilized correctly and within its intended scope. This perspective emphasizes the necessity for AI creators to secure medical malpractice insurance to cover potential damages arising from their innovations. Conversely, when AI serves as an assistive tool, the onus remains on physicians to critically assess AI-generated recommendations, as they retain full responsibility for clinical decisions made [74].

The potential for clinicians to become “liability sinks” in the event of AI-related errors is a pressing concern. Healthcare professionals often feel personally accountable for patient safety incidents, even when such events may be attributed to systemic issues or AI malfunctions. This underscores the importance of defining the extent of clinician responsibility in the context of AI-assisted care [75].

Moreover, the rapid advancement of AI technologies in healthcare necessitates the development of robust regulatory and ethical frameworks. These frameworks are essential to manage safety concerns, privacy issues, and potential biases inherent in AI systems, ensuring that their integration into clinical practice does not compromise patient care standards [76].

In summary, as AI continues to revolutionize medical diagnostics, it is imperative to clearly define the legal and ethical responsibilities of both AI developers and healthcare providers. Such clarity will be instrumental in mitigating legal risks and safeguarding patient well-being in the evolving landscape of AI-enhanced healthcare.

7. Conclusion

The integration of ML into the molecular diagnosis and genotyping of HPV represents a transformative shift in clinical microbiology and public health. While traditional diagnostic methods—such as PCR-based assays and cytological screening—have long been the foundation of HPV detection, they are often constrained by variability in sensitivity, labor-intensive protocols, and reliance on expert interpretation. In contrast, ML-driven approaches offer a highly accurate, automated, and scalable alternative, significantly enhancing diagnostic precision and accessibility.

Over the past decade, ML models—ranging from SVMs and RFs to neural networks—have demonstrated superior diagnostic capabilities in HPV classification, risk stratification, and disease progression modeling. The application of CNN-based architectures for cytological and histopathological image analysis has yielded remarkable improvements in lesion detection accuracy, while hybrid models integrating AI with molecular diagnostics have enabled more precise HPV genotyping. These advances hold particular promise for low-resource settings, where expert pathologists and advanced molecular assays may not be readily available.

Despite these promising developments, several challenges must be addressed before AI-driven HPV diagnostics can be seamlessly integrated into routine clinical workflows. Model generalizability, influenced by dataset diversity and bias, remains a key limitation, necessitating the development of globally representative training datasets. Additionally, the “black-box” nature of many DL models raises concerns about interpretability and clinical trust, underscoring the need for XAI frameworks. Regulatory hurdles further complicate adoption, as AI-based diagnostic tools must undergo rigorous clinical validation and approval processes to ensure safety and reliability.

Looking ahead, future research should focus on developing multi-modal AI systems that integrate genomic, proteomic, and imaging data to enhance diagnostic accuracy. The incorporation of federated learning approaches may mitigate data privacy concerns by enabling collaborative model training without direct data sharing. Furthermore, strengthening ethical frameworks and algorithmic fairness measures will be essential to minimize bias and ensure equitable healthcare outcomes.

In conclusion, ML-based methodologies are poised to revolutionize HPV diagnostics and genotyping, offering a powerful, scalable, and cost-effective solution for early detection and risk stratification. As these technologies continue to evolve, interdisciplinary collaborations between data scientists, microbiologists, and clinicians will be critical in bridging the gap between AI innovation and real-world clinical application. By harnessing the full potential of AI-driven HPV screening and molecular diagnostics, healthcare systems worldwide can take a decisive step toward reducing the burden of HPV-related malignancies and improving global cervical cancer prevention strategies.

Ethical statement:

This review article does not require ethics committee approval or any special permission, as it does not involve human or animal subjects, experiments, or hazardous procedures.

Acknowledgment:

The author declares that no funding was received from any public, commercial, or non-profit organizations. Additionally, there are no competing interests, external support, or advisory influences to disclose.

Conflict of interest:

The author declares that there is no conflict of interest.

Generative AI statement

The author declares that no Gen AI was used in the creation of this manuscript.

Authors' contributions:

The author was solely responsible for the conceptualization, methodology, investigation, formal analysis, and writing of the manuscript. The author read and approved the final version of the manuscript.

References

[1] Arney, A., Bennett, K. M., "Molecular diagnostics of human papillomavirus," *Lab Med.*, vol. 41, no. 9, pp. 523–530, Sep. 2010, doi: 10.1309/LM75WGJSVMI7VVEF.

[2] Williams, J., Kostiuk, M., Biron, V. L., "Molecular detection methods in HPV-related cancers," *Front. Oncol.*, vol. 12, Apr. 2022, doi: 10.3389/fonc.2022.864820.

[3] Abreu, A. L., Souza, R. P., Gimenes, F., Consolaro, M. E., "A review of methods for detecting human papillomavirus infection," *Virol. J.*, vol. 9, Nov. 2012, doi: 10.1186/1743-422X-9-262.

[4] Bosch, F. X., Broker, T. R., Forman, D., et al., "Comprehensive control of human papillomavirus infections and related diseases," *Vaccine*, vol. 31, Suppl. 6, pp. G1–G31, 2013, doi: 10.1016/j.vaccine.2013.10.003.

[5] Alacam, S., Bakir, A., "Human papillomavirus prevalence and genotype distribution in cervical swab samples in Istanbul, Turkey," *J. Infect. Dev. Ctries.*, vol. 15, no. 8, pp. 1190–1196, Aug. 2021, doi: 10.3855/jidc.14663.

[6] Gecer, M., "High-risk human papillomavirus (hrHPV) prevalence and genotype distribution among Turkish women," *J. Cytol.*, vol. 40, no. 1, pp. 42–48, Jan.–Mar. 2023, doi: 10.4103/joc.joc_129_22.

[7] Daponte, N., Valasoulis, G., Michail, G., et al., "HPV-based self-sampling in cervical cancer screening: an updated review of the current evidence in the literature," *Cancers (Basel).*, vol. 15, no. 6, Mar. 2023, doi: 10.3390/cancers15061669.

[8] Drysdale, H., Marlow, L. A. V., Lim, A., Waller, J., "Experiences of self-sampling and future screening preferences in non-attenders who returned an HPV vaginal self-sample in the YouScreen study: findings from a cross-sectional questionnaire," *Health Expect.*, vol. 27, 2024, doi: 10.1111/hex.14118.

[9] Yao, H., Zhang, X., "A comprehensive review for machine learning-based human papillomavirus detection in forensic identification with multiple medical samples," *Front. Microbiol.*, vol. 14, Jul. 2023, doi: 10.3389/fmicb.2023.1232295.

[10] Bartosik, M., Moranova, L., Izadi, N., et al., "Advanced technologies towards improved HPV diagnostics," *J. Med. Virol.*, vol. 96, 2024, doi: 10.1002/jmv.29409.

[11] Vanderveren, E., Debeer, E., Craeynest, M., Hermans, D., Raes, F., "Psychometric properties of the Dutch Cognitive Avoidance Questionnaire," *Psychol. Belg.*, vol. 60, no. 1, pp. 184–197, Jul. 2020, doi: 10.5334/pb.522.

[12] He, S., Xiao, B., Wei, H., Huang, S., Chen, T., "SVM classifier of cervical histopathology images based on texture and morphological features," *Technol. Health Care.*, vol. 31, no. 1, pp. 69–80, 2023, doi: 10.3233/THC-220031.

[13] Ramakrishnan, G., Nori, A., Murfet, H., Cameron, P., "Towards compliant data management systems for healthcare ML," *arXiv [Preprint].*, 2020. [Online]. Available: https://arxiv.org/abs/2011.07555

[14] Varricchio, S., Ilardi, G., Crispino, A., *et al.*, "A machine learning approach to predict HPV positivity of oropharyngeal squamous cell carcinoma," *Pathologica.*, vol. 116, no. 6, 2024, doi: 10.32074/1591-951X-1027.

[15] Chen, X., Aljrees, T., Umer, M., *et al.*, "Cervical cancer detection using K nearest neighbor imputer and stacked ensemble learning model," *Digit. Health.*, vol. 9, Oct. 2023, doi: 10.1177/20552076231203802.

[16] Zammataro, L., "CINNAMON-GUI: Revolutionizing Pap Smear Analysis with CNN-Based Digital Pathology Image Classification," *F1000Res.*, vol. 13, Aug. 2024, doi: 10.12688/f1000research.154455.1.

[17] Santa, S., Kwofie, S. K., Agyenkwa-Mawuli, K., et al.,"Prediction of human papillomavirus-host oncoprotein interactions using deep learning," *Bioinform. Biol. Insights.*, vol. 18, 2024, doi: 10.1177/11779322241304666.

[18] Jia, F., Li, S., Zhang, T., "Detection of cervical cancer cells based on strong feature CNN-SVM network," *Neurocomputing.*, vol. 411, 2020, doi: 10.1016/j.neucom.2020.06.006.

[19] Darwish, M., Altabel, M. Z., Abiyev, R. H., “Enhancing cervical pre-cancerous classification using advanced vision transformer,” *Diagnostics (Basel).*, vol. 13, no. 18, 2023, doi: 10.3390/diagnostics13182884.

[20] Yilmaz, A., Demircali, A. A., Kocaman, S., Uvet, H., “Comparison of deep learning and traditional machine learning techniques for classification of Pap smear images,” *arXiv [Preprint].*, 2020. [Online]. Available: https://arxiv.org/abs/2009.06366

[21] Lang, D. M., Peeken, J. C., Combs, S. E., Wilkens, J. J., Bartzsch, S., “Deep learning-based HPV status prediction for oropharyngeal cancer patients,” *arXiv [Preprint].*, 2020. [Online]. Available: https://arxiv.org/abs/2011.08555

[22] Ma, Y., Xu, T., Huang, X., *et al.*, “Computer-aided diagnosis of label-free 3-D optical coherence microscopy images of human cervical tissue,” *IEEE Trans. Biomed. Eng.*, vol. 66, no. 9, pp. 2447–2456, 2019, doi: 10.1109/TBME.2018.2890167.

[23] Liu, W., Li, C., Xu, N., *et al.*, “CVM-Cervix: A hybrid cervical Pap-smear image classification framework using CNN, visual transformer, and multilayer perceptron,” *arXiv [Preprint].*, 2022. [Online]. Available: https://arxiv.org/abs/2206.00971

[24] Ince, O., Uysal, E., Durak, G., et *al.*, “Prediction of carcinogenic human papillomavirus types in cervical cancer from multiparametric magnetic resonance images with machine learning-based radiomics models,” *Diagn. Interv. Radiol.*, vol. 29, no. 3, pp. 460–468, May 2023, doi: 10.4274/dir.2022.221335.

[25] Sornapudi, S., Brown, G. T., Xue, Z., et al., “Comparing deep learning models for multi-cell classification in liquid-based cervical cytology images,” *arXiv [Preprint].*, 2019. [Online]. Available: https://arxiv.org/abs/1910.00722

[26] Kularathne, Y., Janitha, P., Ambepitiya, S., et al., “SynthVision – Harnessing minimal input for maximal output in computer vision models using synthetic image data,” *arXiv [Preprint].*, 2024. [Online]. Available: https://arxiv.org/abs/2402.02826

[27] Zhang, L., Lu, L., Nogues, I., et al., “DeepPap: Deep convolutional networks for cervical cell classification,” *IEEE J. Biomed. Health Inform.*, vol. 21, no. 6, pp. 1633–1643, 2017, doi: 10.1109/JBHI.2017.2705583.

[28] Rahaman, M. M., Li, C., Yao, Y., *et al.*, “DeepCervix: A deep learning-based framework for the classification of cervical cells using hybrid deep feature fusion techniques,” *Comput. Biol. Med.*, vol. 136, 2021, doi: 10.1016/j.compbiomed.2021.104649.

[29] Uehara, S., Kobayashi, M., Kimura, K., Suzuki, J., Sadamasu, K., “Rapid identification of histamine-producing bacteria isolated from fish using MALDI-TOF MS,” *J. Food Sci. Technol.*, vol. 58, no. 10, pp. 4055–4061, Oct. 2021, doi: 10.1007/s13197-021-05092-7.

[30] Lomsadze, A., Li, T., Rajeevan, M. S., Unger, E. R., Borodovsky, M., “Bioinformatics pipeline for human papillomavirus short read genomic sequences classification using support vector machine,” *Viruses.*, vol. 12, no. 7, p. 710, Jun. 2020, doi: 10.3390/v12070710.

[31] Asensio-Puig, L., Alemany, L., Pavón, M., “A straightforward HPV16 lineage classification based on machine learning,” *Front. Artif. Intell.*, vol. 5, p. 851841, Jun. 2022, doi: 10.3389/frai.2022.851841.

[32] Tanchotsrinon, W., Lursinsap, C., Poovorawan, Y., “A high performance prediction of HPV genotypes by Chaos game representation and singular value decomposition,” *BMC Bioinformatics*, vol. 16, p. 71, Mar. 2015, doi: 10.1186/s12859-015-0493-4.

[33] Senthilkumar, R., Al Musleh, M., “Smart temperature-controlled infant car seat using thermoelectric devices,” in *Proc. IEEE Int. IEMTRONICS Conf.*, Vancouver, BC, Canada, Sep. 2020, pp. 1–7, doi: 10.1109/IEMTRONICS51293.2020.9216387.

[34] Klein, S., Wuerdemann, N., Demers, I., et al., “Predicting HPV association using deep learning and regular H&E stains allows granular stratification of oropharyngeal cancer patients,” *NPJ Digit. Med.*, vol. 6, p. 152, 2023, doi: 10.1038/s41746-023-00901-z.

[35] Geeitha, S., Renuka, P., Thilagavathi, C., et al., “LSTM - Recurrent neural network model to forecast the risk factors in recurrent cervical carcinoma,” in *Proc. Int. Conf. Self Sustain. Artif. Intell. Syst. (ICSSAS)*, Erode, India, Jan. 2024, pp. 132–137, doi: 10.1109/ICSSAS64001.2024.10760386.

[36] Li, P., Wang, X., Liu, P., et al., “Cervical lesion classification method based on cross-validation decision fusion method of vision transformer and DenseNet,” *J. Healthc. Eng.*, vol. 2022, p. 3241422, May 2022, doi: 10.1155/2022/3241422.

[37] Cheng, S., Liu, S., Yu, J., et al., “Robust whole slide image analysis for cervical cancer screening using deep learning,” *Nat. Commun.*, vol. 12, no. 1, p. 5639, 2021, doi: 10.1038/s41467-021-25296-x.

[38] Shakil, R., Islam, S., Akter, B., “A precise machine learning model: Detecting cervical cancer using feature selection and explainable AI,” *J. Pathol. Inform.*, vol. 15, p. 100398, Sep. 2024, doi: 10.1016/j.jpi.2024.100398.

[39] Zhai, F., Mu, S., Song, Y., et al., “Machine learning prediction of residual and recurrent high-grade CIN post-LEEP,” *Cancer Manag. Res.*, vol. 16, pp. 1175–1187, 2024, doi: 10.2147/CMAR.S484057.

[40] Wong, O. G. W., Ng, I. F. Y., Tsun, O. K. L., et al., “Machine learning interpretation of extended human papillomavirus genotyping by Onclarity in an Asian cervical cancer screening population,” *J. Clin. Microbiol.*, vol. 57, no. 12, p. e00997-19, Nov. 2019, doi: 10.1128/JCM.00997-19.

[41] Remita, M. A., Halioui, A., Diouara, A. A. M., et al., “A machine learning approach for viral genome classification,” *BMC Bioinformatics*, vol. 18, no. 1, p. 208, Apr. 2017, doi: 10.1186/s12859-017-1602-3.

[42] Hou, X., Shen, G., Zhou, L., Li, Y., Wang, T., Ma, X., “Artificial intelligence in cervical cancer screening and diagnosis,” *Front. Oncol.*, vol. 12, p. 851367, Mar. 2022, doi: 10.3389/fonc.2022.851367.

[43] Crowson, M. G., Moukheiber, D., Arévalo, A. R., et al., “A systematic review of federated learning applications for biomedical data,” *PLOS Digit. Health*, vol. 1, no. 5, p. e0000033, May 2022, doi: 10.1371/journal.pdig.0000033.

[44] Doshi-Velez, F., Kim, B., “Towards a rigorous science of interpretable machine learning,” *arXiv preprint*, 2017. Available: https://arxiv.org/abs/1702.08608.

[45] Dellino, M., Cerbone, M., d’Amati, A., et al., “Artificial intelligence in cervical cancer screening: Opportunities and challenges,” *AI*, vol. 5, no. 4, pp. 2984–3000, 2024, doi: 10.3390/ai5040144.

[46] Mehrabi, N., Morstatter, F., Saxena, N., Lerman, K., Galstyan, A., “A survey on bias and fairness in machine learning,” *ACM Comput. Surv.*, vol. 54, no. 6, Article 115, 2021, doi: 10.1145/3457607.

[47] Gichoya, J. W., Banerjee, I., Bhimireddy, A. R., et al., “AI recognition of patient race in medical imaging: A modelling study,” *Lancet Digit. Health*, vol. 4, no. 6, pp. e406–e414, Jun. 2022, doi: 10.1016/S2589-7500(22)00063-2.

[48] Arora, A., Alderman, J. E., Palmer, J., et al., “The value of standards for health datasets in artificial intelligence-based applications,” *Nat. Med.*, vol. 29, no. 11, pp. 2929–2938, Nov. 2023, doi: 10.1038/s41591-023-02608-w.

[49] Rieke, N., Hancox, J., Li, W., et al., “The future of digital health with federated learning,” *NPJ Digit. Med.*, vol. 3, p. 119, Sep. 2020, doi: 10.1038/s41746-020-00323-1.

[50] Kaissis, G., Ziller, A., Passerat-Palmbach, J., et al., “End-to-end privacy preserving deep learning on multi-institutional medical imaging,” *Nat. Mach. Intell.*, vol. 3, no. 6, pp. 473–484, 2021, doi: 10.1038/s41563-021-00838-z.

[51] Chandra Sekar, P. K., Thomas, S. M., Veerabathiran, R., “The future of cervical cancer prevention: Advances in research and technology,” *Explor. Med.*, vol. 5, pp. 384–400, 2024. doi: 10.37349/emed.2024.00226

[52] Wu, E., Wu, K., Daneshjou, R., et al., “How medical AI devices are evaluated: Limitations and recommendations from an analysis of FDA approvals,” *Nat. Med.*, vol. 27, no. 4, pp. 582–584, 2021. doi: 10.1038/s41591-021-01312-x

[53] Ahmed, M. I., Spooner, B., Isherwood, J., et al., “A systematic review of the barriers to the implementation of artificial intelligence in healthcare,” *Cureus*, vol. 15, no. 10, p. e46454, 2023. doi: 10.7759/cureus.46454

[54] Wang, R., Gunesli, G. N., Skingen, V. E., et al., “Deep learning for predicting prognostic consensus molecular subtypes in cervical cancer from histology images,” *NPJ Precis. Oncol.*, vol. 9, no. 1, p. 11, 2025. doi: 10.1038/s41571-024-00955-3

[55] Egemen, D., Perkins, R. B., Cheung, L. C., et al., “Artificial intelligence–based image analysis in clinical testing: lessons from cervical cancer screening,” *J. Natl. Cancer Inst.*, vol. 116, no. 1, pp. 26–33, 2024. doi: 10.1093/jnci/djad202

[56] Wu T., Lucas E., Zhao F., Basu P., and Qiao Y., "Artificial intelligence strengthens cervical cancer screening – present and future," *Cancer Biol. Med.*, 2024. doi: 10.20892/j.issn.2095-3941.2024.0198

[57] Xiao, T., Wang, C., Yang, M., et al., “Use of virus genotypes in machine learning diagnostic prediction models for cervical cancer in women with high-risk human papillomavirus infection,” *JAMA Netw. Open*, vol. 6, no. 8, p. e2326890, 2023. doi: 10.1001/jamanetworkopen.2023.26890

[58] Ma, C. H., Li, L., Cai, S., et al., “Development of an HPV genotype detection platform based on aggregation-induced emission (AIE) and flow-through hybridization technologies,” *Molecules*, vol. 27, no. 20, p. 7036, 2022. doi: 10.3390/molecules27207036

[59] Stegmüller, T., Abbet, C., Bozorgtabar, B., et al., “Self-supervised learning-based cervical cytology for the triage of HPV-positive women in resource-limited settings and low-data regime,” *arXiv preprint*, 2023. [Online]. Available: https://arxiv.org/abs/2302.05195

[60] Wang R., Khurram S. A., Asif A., Young L., Rajpoot N., "Rank the triplets: a ranking-based multiple instance learning framework for detecting HPV infection in head and neck cancers using routine H&E images," *arXiv*, 2022. [Online]. Available: https://arxiv.org/abs/2206.08275

[61] Chen, K., Wang, Q., & Ma, Y., "Cervical optical coherence tomography image classification based on contrastive self-supervised texture learning," *Med. Phys.*, vol. 49, no. 6, pp. 3638–3653, 2022. doi: 10.1002/mp.15630

[62] Murdoch, B., "Privacy and artificial intelligence: challenges for protecting health information in a new era," *BMC Med. Ethics*, vol. 22, p. 122, 2021. doi: 10.1186/s12910-021-00687-3

[63] de Filippis, R., Al Foysal, A., Rocco, V., et al., "The risk perspective of AI in healthcare: GDPR and GELSI framework (Governance, Ethical, Legal and Social Implications) and the new European AI Act," *Ital. J. Psychiatry*, vol. 10, no. 1, 2024. doi: 10.36180/2421-4469-2024-4

[64] Wang C., Zhang J., Lassi N., Zhang X., "Privacy protection in using artificial intelligence for healthcare: Chinese regulation in comparative perspective," *Healthcare (Basel)*, vol. 10, no. 10, p. 1878, 2022. doi: 10.3390/healthcare10101878.

[65] Mittermaier M., Raza M. M., and Kvedar J. C., "Bias in AI-based models for medical applications: challenges and mitigation strategies," NPJ Digit. Med., vol. 6, p. 113, 2023. doi: 10.1038/s41746-023-00858-z.

[66] Colón-Rodríguez C. J., "Shedding light on healthcare algorithmic and artificial intelligence bias," Office of Minority Health, U.S. Department of Health and Human Services, 2023. [Online]. Available: https://minorityhealth.hhs.gov/news/shedding-light-healthcare-algorithmic-and-artificial-intelligence-bias. [Accessed: Feb. 26, 2025].

[67] Abràmoff, M. D., Tarver, M. E., Loyo-Berrios, N., et al., "Considerations for addressing bias in artificial intelligence for health equity," *NPJ Digit. Med.*, vol. 6, no. 1, p. 170, 2023. doi: 10.1038/s41746-023-00869-7

[68] Abgrall, G., Holder, A. L., Chelly Dagdia, Z., Zeitouni, K., & Monnet, X., "Should AI models be explainable to clinicians?," *Crit. Care*, vol. 28, no. 1, p. 301, 2024. doi: 10.1186/s13054-024-05005-y

[69] Amann, J., Vetter, D., Blomberg, S. N., et al., "To explain or not to explain?—Artificial intelligence explainability in clinical decision support systems," *PLOS Digit. Health*, vol. 1, no. 2, p. e0000016, 2022. doi: 10.1371/journal.pdig.0000016

[70] Amann J., Blasimme A., Vayena E., Frey D., Madai V.I., "Explainability for artificial intelligence in healthcare: a multidisciplinary perspective," BMC Med. Inform. Decis. Mak., vol. 20, no. 1, p. 310, 2020. doi: 10.1186/s12911-020-01332-6

[71] Hill, D. L. G., "AI in imaging: the regulatory landscape," *Br. J. Radiol.*, vol. 97, no. 1155, pp. 483–491, 2024. doi: 10.1093/bjr/tqae002

[72] Palaniappan K., Lin E.Y.T., Vogel S., "Global regulatory frameworks for the use of artificial intelligence (AI) in the healthcare services sector," Healthcare (Basel), vol. 12, no. 5, p. 562, 2024. doi: 10.3390/healthcare12050562

[73] Sidharthan C., Cheriyedath S., "FDA strengthens AI regulation to ensure patient safety and innovation in healthcare," News Med., Oct. 16, 2024. [Online]. Available: https://www.news-medical.net/news/20241016/FDA-strengthens-AI-regulation-to-ensure-patient-safety-and-innovation-in-healthcare.aspx [Accessed: Feb. 26, 2025].

[74] Cestonaro C., Delicati A., Marcante B., Caenazzo L., Tozzo P., "Defining medical liability when artificial intelligence is applied on diagnostic algorithms: a systematic review," Front. Med. (Lausanne), vol. 10, p. 1305756, 2023, doi: 10.3389/fmed.2023.1305756.

[75] Lawton, T., Morgan, P., Porter, et al., "Clinicians risk becoming 'liability sinks' for artificial intelligence," *Future Healthc. J.*, vol. 11, no. 1, p. 100007, 2024. doi: 10.1016/j.fhj.2024.100007

[76] Egan D., Ji J., "AI in healthcare: legal and ethical considerations in this new frontier," [Online]. Available: https://www.ibanet.org/ai-healthcare-legal-ethical [Accessed: Feb. 26, 2025].