AI

Review

Artificial Intelligence in Cervical Cancer Screening: Opportunities and Challenges

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Abstract: Among gynecological pathologies, cervical cancer has always represented a health problem with great social impact. The giant strides made as a result of both the screening programs perfected and implemented over the years and the use of new and accurate technological equipment have in fact significantly improved our clinical approach in the management and personalized diagnosis of precancerous lesions of the cervix. In this context, the advent of artificial intelligence and digital algorithms could represent new directions available to gynecologists and pathologists for the following: (i) the standardization of screening procedures, (ii) the identification of increasingly early lesions, and (iii) heightening the diagnostic accuracy of targeted biopsies and prognostic analysis of cervical cancer. The purpose of our review was to evaluate to what extent artificial intelligence can be integrated into current protocols, to identify the strengths and/or weaknesses of this method, and, above all, determine what we should expect in the future to develop increasingly safer solutions, as well as increasingly targeted and personalized screening programs for these patients. Furthermore, in an innovative way, and through a multidisciplinary vision (gynecologists, pathologists, and computer scientists), with this manuscript, we highlight a key role that AI could have in the management of HPV-positive patients. In our vision, AI will move from being a simple diagnostic device to being used as a tool for performing risk analyses of HPV-related disease progression. This is thanks to the ability of new software not only to analyze clinical and histopathological images but also to evaluate and integrate clinical elements such as vaccines, the composition of the microbiota, and the immune status of patients. In fact, the single-factor evaluation of high-risk HPV strains represents a limitation that must be overcome. Therefore, AI, through multifactorial analysis, will be able to generate a risk score that will better stratify patients and will support clinicians in choosing highly personalized treatments overall. Our study remains an innovative proposal and idea, as the literature to date presents a limitation in that this topic is considered niche, but we believe that the union of common efforts can overcome this limitation.

Keywords: artificial intelligence; AI; cervical cancer screening; cervical cancer; HPV; cervical intraepithelial neoplasia

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1. Background

Persistent infection with carcinogenic genotypes of human papilloma virus (HPV) is the primary driver of cervical cancer (CC), with a disease pathway from initial infection through precancerous stages to invasive disease [1,2]. The understanding of this causal progression has been essential for the concentration of screening strategies and for a reduction in the morbidity and mortality of this disease. In recent years, we have witnessed the reprogramming of screening levels for CC, and this is essentially due to the greater reliability of the HPV-DNA test compared to cytological examination (Pap test). Nonetheless, this method is not uniformly used worldwide both for economic reasons and due to the absence of highly specialized personnel. It is, therefore, urgently required to find new strategies to make up for this deficiency. Artificial intelligence (AI) is changing the way clinicians diagnose and treat pathologies [3–5]. In this review, we aim to elucidate the possible pragmatic application of AI algorithms to the real-life experience of clinicians; in our research, we applied a translational approach, collaborating in a multidisciplinary team with the Computer Science Department of our University. This direct collaboration aimed to fill the gap that is still the subject of debate between theoretical AI and everyday clinical practice [6,7]. The application of AI algorithms to colposcopy could provide new insight to clinicians in the diagnosis and treatment of complex disease and in preventing CC [8,9]. Nowadays, AI has numerous applications across various fields, especially in healthcare. Over time, advancements in AI have reduced the workload of professionals, particularly where there is a shortage of specialists. First, AI plays a significant role in image analysis for the early detection of cervical cancer, helping to prevent patient mortality through timely diagnosis. Second, AI can analyze data from HPV tests, combined with patient history, to predict individual risk levels, aiding in personalized patient care. Third, AI enables remote colposcopy diagnosis. In low-resource and rural areas where it is challenging to conduct in-person colposcopy exams, AI allows specialists to review images taken remotely. Fourth, AI assists radiologists in staging cervical cancer, which is crucial for determining a patient's treatment plan. This support enhances radiology staging accuracy and treatment planning. Finally, each case of cervical cancer is unique. AI can personalize treatment by predicting patient responses to specific therapies, allowing for more tailored approaches that make treatments more effective. In addition, to protect patients' privacy regarding their personal health data records and to increase the performance of ML, federated learning (FL) is very crucial; this is used to train models without sharing data in hospitals. Federated learning (FL) enables ML models to perform very well and increases the privacy preservation of patients' health record data. Technical terms are defined in the Glossary.

2. AI, Machine Learning, and Deep Learning in Medicine: An Overview

The term AI was defined in 1956 in the Dartmouth Summer Research Project workshop by a group of scientists led by Professor John McCarthy. In this first meaning, AI was defined as any form of automation that could simulate human intellectual tasks and human learning [10]. Jackson, in the book *Introduction to Artificial Intelligence*, defined AI as "the ability of machines to do things that people would say require intelligence" [11–13]. In recent years, there has been an emerging use of artificial intelligence in medicine in software that matches clinical findings with the stored profiles of diseases. This approach is used in a preliminary phase of the automatic interpretation of anomalous ECG patterns that can help clinicians diagnose complex clinical conditions. Promising studies on the application of AI in the cardiologic clinical context have emerged on heart failure and atrial fibrillation [14,15]. Since computers were first invented, computer programming has been based on algorithms. An algorithm is a sequence of instructions that can transform an input into an output. This approach has been applied to increasingly complex problems of our everyday life. For some tasks, including everyday ones, such as recognizing people in photographs, driving cars, or holding conversations in different languages, we do not have a satisfying algorithm despite decades of research, although we do have data [16]. The idea of machine learning (ML) is to program computers to use data to construct a good and useful model of the problem in order to make predictions about its most probable solutions [3]. There are two broad categories of ML: supervised and unsupervised [17,18]. In supervised learning, the computer is trained with known inputs and the corresponding outputs: its task is to build an optimal model that matches input and outputs; the model is then applied to unknown inputs to classify them and generate the probable corresponding output. In unsupervised learning, the computer is presented with only inputs; its task is to elaborate an optimal model that clusters or groups the data. Other promising forms of ML are based on the concept of reinforcement learning [19]. One of the hot topics of ML is in human pathology, where pathological slides are converted into digital images from which software extracts features and labels. The main limitation of traditional ML is the large amount of data needed for training; the few-shot and one-shot ML models have tried to overcome this problem with a Bayesian framework, but currently, the applications are quite specific, and these approaches are less effective than traditional ML [20]. The term "big data" (BD) defines datasets with sizes beyond the computational power of commonly used software, meaning that parallel computer tools are needed to handle them. However, from a different perspective, BD can also be defined according to the domain of knowledge rather than to the data size, in the sense that if, ideally, all the data about a specific disease were collected in a single storage space, that knowledge would represent the "ground truth" (also known as gold truth) for the given disease. Big data tools are able to make sense of data and transform them into human understandable knowledge [19]. The classical definition of big data comprises the 5 Vs: volume, variety, velocity, veracity, and value [21,22]. BD capture, store, and elaborate huge amounts of data (volume) in structured, semi-structured, and unstructured forms (variety), generated in a high-speed process (velocity). These data are characterized by high truthfulness (veracity) and high profitability (value) [23]. Deep learning (DL) is a subset of machine learning based on multiple layers in the network that progressively extract features from unstructured raw data. Modern DL is based on multi-layer structures connected like biological neurons. In some clinical contexts, the implementation of AI tools in everyday clinical decisions has led to advancements in diagnosis, treatment personalization, and overall health management. The diffusion of AI tools is potentially able to reduce diagnostic errors and improve the detection rates of multiple diseases. AI for mammogram interpretation, for example, reduced false positive rates by 5.7% and false negative rates by 9.4%, thus being more accurate than expert radiologists in terms of accuracy for detecting early-stage breast cancer (91% vs. 74%) [24,25]. AI-driven deep learning models also perform well in dermatology, accurately diagnosing melanoma and recommending treatments similar to dermatologist assessments [26–28]. Another interesting application is the use of an AI algorithm in the diagnosis of acute appendicitis, which showed 83.75% accuracy, aiding timely surgical decisions [29]. A high-impacting sector for AI studies is precision medicine in cancer care, with a potential role in the prediction of the response to chemotherapy in specific cohorts of patients, but the applications of those algorithms are still experimental [30,31]. A further field of interest of AI is in the predictive analytics of population data for early intervention in chronic disease prevention, such as cardiac or endocrine disease [32].

3. AI to Fill Gaps in Cervical Cancer Screening

Today, the gold standard for the prevention of CC is based on two main strategies. The first, also called the "primary" strategy, involves the use of anti-HPV vaccines in order to prevent infections that can progress into precancerous lesions related to HPV [33]. The second develops through screening protocols that are increasingly codified at an international level [34]. In the first case, there are several studies that have shown that bivalent and quadrivalent vaccines targeting high-risk HPV serotypes have very high efficacy against persistent carcinogenic infections, greater than 90% compared to a placebo [35,36]. Secondary prevention, on the other hand, includes various clinical pillars and makes use of the Pap test and the HPV-DNA test [37], which, according to the most recent guidelines, should be prescribed globally, regardless of the availability of resources [38]. In fact, given its lower sensitivity, the Pap test is recommended by the World Health Organization [39] and other guidelines only as a secondary test [40,41]. Indeed, this method presents considerable variability among different observers, as well as the proven risk of false negatives [42]. This disadvantage also emerges from a robust randomized study, which highlighted the limitation of the Pap test compared to the HPV-DNA test [43] in the identification of early high-grade lesions of the cervix. In patients with a positive or abnormal HPV-DNA test result, colposcopy is indicated and is considered a fundamental test in monitoring women over time [38]. Nonetheless, this strategy requires a significant effort from the point of view of ultra-specialist training, the procurement of equipment, and high costs that may not allow its use on a large scale. Goldie et al. proposed, from a cost-effective perspective, a screening focused on two steps: the HPV-DNA test executed at the age of the peak number of infections (35 or 35–40 years) and direct treatment of HPV-positive women with cryo-therapy [44]. The main advantage of this strategy is the possible see-and-treat of cervical intraepithelial lesions (CIN) in low-resource settings. However, given the crucial role of persistent HPV infection in CC, the problem remains regarding access to large-scale screening protocols for targeted and timely treatment. In this complex context, the implementation of software for the automated analysis of colposcopy and Pap test images could represent a turning point by simplifying, standardizing, and implementing the procedures, as well as being able to progressively reduce the costs of new customized workflows.

AI and Colposcopy in Cervical Cancer Screening

Colposcopy is a widely prescribed exam in low-and-middle-income countries (LMICs) as the second level after an abnormal pap smear/HPV test. It aims to diagnose CIN and execute cervical biopsies targeted to the sites [45,46]. However, in most countries, the overall performance of this exam remains unsatisfactory due to the lack of targeted proposed minimum and comprehensive quality measures. The overall performance of colposcopy remains unsatisfactory [47]. The diagnostic sensitivity of CIN2 is reported to be 30–70% [48,49]. To increase the diagnostic accuracy of colposcopy, some authors have proposed to increase the number of biopsies or to use a random sampling of apparently disease-free cervixes [50]. The use of random biopsies found high-grade lesions in 13–37% of the cases [51,52]. In LMICs, colposcopy has low accuracy due to a lack of experience in operator and colposcopy training courses, low-quality chemical staining, and the lack of consensus on features and guidelines. The diagnostic accuracy for cervical biopsy to detect CINs is relatively low, ranging from 30% to 70%, especially in LMICs, due to low colposcopy capability [53]. The sensitivity and specificity of senior colposcopists to diagnose CIN 2 are up to 80% and 71%, respectively. However, junior colposcopists have difficulty detecting many cases of CIN2 or even CC. For junior colposcopists, their sensitivity and specificity in CIN2 were 59% and 76%, respectively [54]. The digitalization of gynecologic equipment and the implementation of digital colposcopy may help to generate high-quality images for the diagnostic software while maintaining a lower cost and a higher availability with respect to a well-trained colposcopy specialist. In this sense, AI may contribute to fill the gap. In particular, deep learning can extrapolate features of cervical lesions and generate the input for computer-assisted colposcopy exams. The diagnostic workflow of colposcopy should be integrated with AI for evaluating biopsy spots. In Figure 1, we describe a potential AI-enhanced colposcopy workflow. Some pilot studies have implemented retrospectives studies in ML-based cervical cancer screening [8].

Two relevant studies for the detection of CIN2 were conducted by Kim and Song [55,56] using digital cervicography, a technique introduced by Stafl in 1981 [57] in which non-medical staff can acquire a digital picture to be analyzed at a later date by a clinician. Kim trained an automatic cervigram image analysis system with a support vector machine technique to isolate the region of interest and ultimately classify the image as benignant/CIN1 or CIN2 [56]. The proposed system achieved a sensitivity and specificity of 75% in detecting CIN2 from 1000 normal and 1000 CIN1 images for a training set of 2000 images [56]. Hu et al. trained an ML system to detect CIN2 on 9127 patients with a more robust technique:

a training set of 9406 pictures was used to validate an ML algorithm [58]. On a validation set of 344 patients, their algorithm showed an area under the curve of 0.91 in the detection of CIN2. Song et al. trained a multimodal convolutional neural network to detect CIN2 on a training set of 7811 cervical images and clinical data collected by the National Cancer Institute in the Guanacaste dataset. They tested the protocol on 280 patients with CIN1 (n = 140) and CIN2 (n = 140). The results showed accuracy, sensitivity, and specificity of around 89%, 83% and 94%, respectively. Miyagi et al., in 2019, used 253 images taken from traditional colposcopy of patients who underwent cervical biopsy combined with HPV testing to train their ML algorithm [59]. They randomly divided the images, using 80% for training and 20% for testing. The sensitivity and specificity were about 95% and 83%. Asiedu et al. trained an ML system with 2000 colposcopy images and retrospectively classified 134 patient images retrieved from a pocket colposcope with sensitivity, specificity, and accuracy of about 81%, 78%, and 80%, respectively, in distinguishing CIN2 from normal tissue [60]. Simoes analyzed 170 images retrieved from a pocket colposcope with an artificial neural network and classified 58 images with an accuracy of 72%, a sensitivity of 69%, and a specificity of 68% [61]. Overall, the studies represented in Table 1 indicate an encouraging trajectory, but they cannot be generalized due to the relatively small training set and lack of external validations/prospective clinical trials to confirm the results in clinical settings. In the future, we expect more medical evidence to unlock the enigma of ML-guided digital colposcopy.

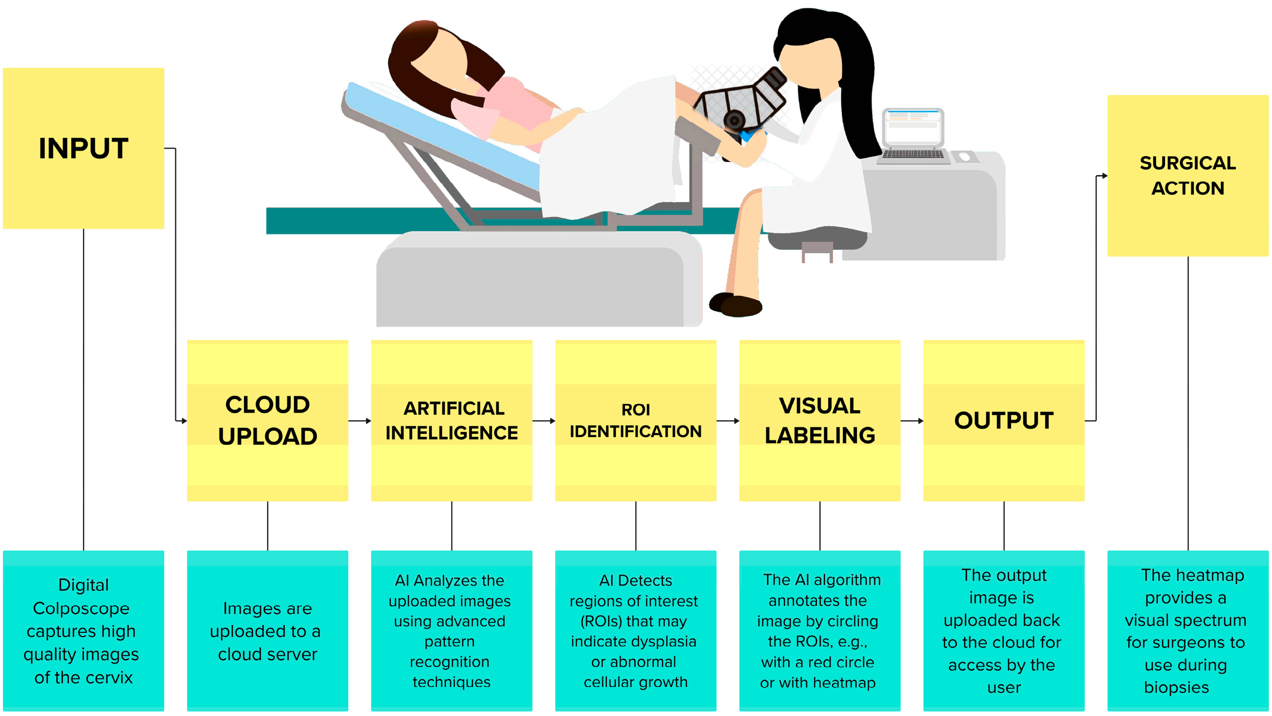

Figure 1. Diagnostic workflow of colposcopy integrated with AI for evaluating biopsy spots. The figure depicts a schematic representation of the role of AI in guiding surgeons during cervical biopsy procedures to target areas with a higher probability of dysplasia. The image of the cervix is given to the AI algorithm. The algorithm analyzes the image with pattern recognition techniques and identifies regions of interest indicative of dysplasia or abnormal cell growth. The final step is a final image that highlights areas of probable dysplasia. This mapping is depicted through a gradient of color that represents a heatmap of a spectrum of probabilities assigned to different regions of the cervix that the surgeon can use as a visual aid for oriented biopsy procedures.

Table 1. General characteristics of main studies on AI colposcopy.

Paper ID	Year	Methods	Image Source	Classification	Training Dataset (n. Images)	Test Dataset (n. Images)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
[60]	2019	SVM	DC	Binary *	62	134	81.30	78.60	80.00	NR
[62]	2021	CNN	OCI	Binary *	7498	1884	92.40	96.20	92.30	/
[63]	2023	CNN	SC	Binary *	6002	1200	93.60	87.60	90.61	0.96
[64]	2022	SVM	OCI	Binary *	6564	894	80.98	77.56	61.97	0.874
[65]	2020	CNN	OCI	Binary *,**	675	116	85.20	88.20	87.7	0.947
[58]	2019	Faster-CNN	CG	Binary *	744	9406	NR	NR	NR	0.91
[66]	2013	SVM	CG	Binary *	939	2000	75.00	76.00	NR	NR
[55]	2022	Cerviray AI®	DC	Normal, CIN1, CIN2, CIN3, cancer	NR	234	74.14	83.05	NR	0.77
[67]	2023	DeepLabv3+, Google ©	DC	Binary *	1554	777	87.20	90.10	93.20	NR
[59]	2019	CNN	OCI	Binary *	NR	253	95.60	NR	83.30	0.963
[68]	2021	CNNvgg16	DC	Binary *	300	60	84.10	89.80	86.30	NR
[55]	2015	Multi-CNN	CG	Binary *	939	280	83.21	94.79	80.00	NR
[69]	2023	CAIADS	DC	Normal, CIN2, CIN3, cancer	NR	366	CIN2 95.10CIN3 85.30CANCER 95.80	CIN2 48.30CIN3 43.90CANCER 38.30	NR	CIN2 0.717CIN3 0.70CANCER 0.67
[70]	2020	CAIADS	DC	Binary *	13,604	3887	LSIL 90.50 HSIL 71.90	LSIL 51.80	HSIL 93.90	NR
[71]	2020	CNN	DC	Binary *	8292	1036	85.38	82.62	84.10	0.93
[72]	2020	CNN	CG	Normal, CIN1, CIN2	NR	4753	95.09	98.22	96.13	0.94
[73]	2022	Visualcheck, EVA ©	OCI	Binary *	NR	48	66.70	46.7	NR	NR

Abbreviations: CNN: Convolutional Neural Network, SVM: Support Vector Machine, CAIADS: Colposcopic Artificial Intelligence Auxiliary Diagnostic System, DC: Digital Colposcope, CG: Cervicography, OCI: Optical Colposcope Image, Classification: * CIN1 vs. CIN2, ** needing biopsy vs. not needing biopsy, AUC: Area Under the Curve, NR: Not Reported.

4. Materials and Methods

A narrative review of AI in colposcopy was performed through a literature search in the following electronic databases: PubMed, the Cochrane Library, Embase, Web of Science, and Medline (Figure 2). The article research was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. The following search terms were used: "Artificial Intelligence", "cervical cancer" "cervical intraepithelial neoplasia", " HPV". Original quantitative research articles that explicitly described the application of ML in the classification of colposcopy images of the cervix in correlation with histology and histopathology were included. In contrast, articles that did not have the full text available and articles whose study objectives did not answer the research question were excluded. No restrictions on the publication period were applied. Additionally, we considered only reviews published in English. The titles and abstracts of the eligible articles were independently reviewed by four authors (M.D., M.C., E.C. (Eliano Cascardi), and G.C.). Duplicates were removed. The full texts of potentially suitable studies were independently assessed for eligibility by the two authors (M.D. and E.C. (Eliano Cascardi)). Any discordance between the two sides was solved through discussion with two senior reviewers (V.P. and E.C. (Ettore Cicinelli)). Data were retrieved from articles published in a 20-year period between January 2004 and October 2024.

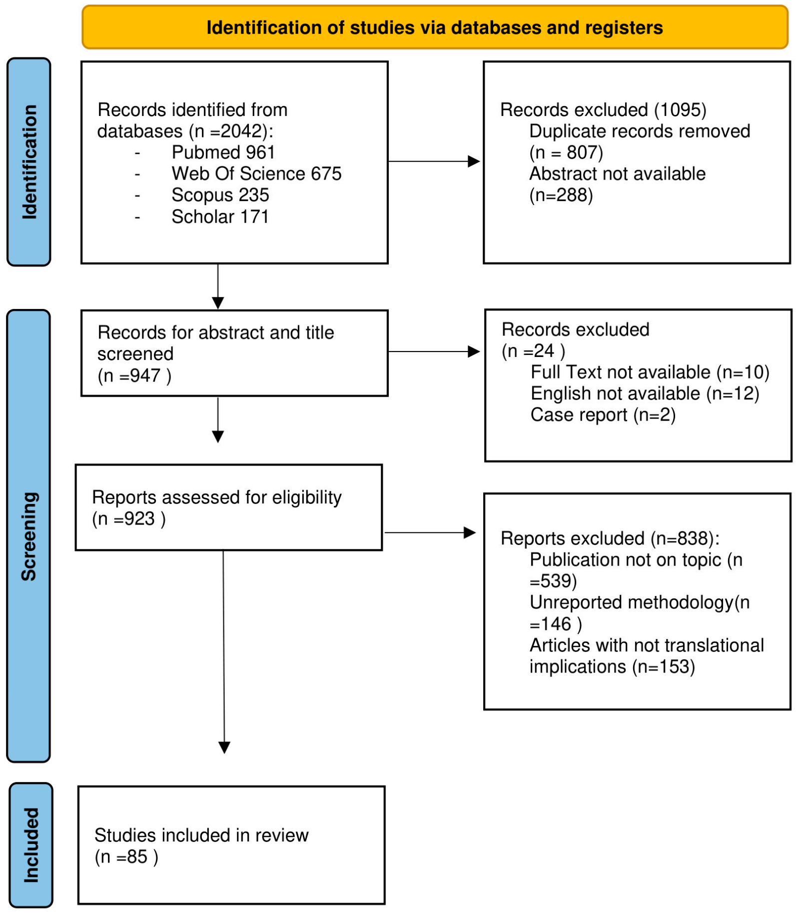

Figure 2. Study flow diagram: PRISMA flow diagram of identification, screening, and inclusion of articles. Systematic literature reviews were selected with standard methods to be briefly presented in the article.

5. Results

From the literature search, we identified 85 publications comprising 68 reviews and a total of 17 original articles, as listed in Table 1.

The findings from Table 1 offer a glimpse into the evolving landscape of ML-guided digital colposcopy. The methods employed by the researchers include support vector machine (SVM), convolutional neural network (CNN), and other innovative AI algorithms. Certain studies showed high sensitivity, specificity, accuracy, and area under the curve. However, challenges such as small training datasets, variations in image quality, and the complexity of cervical tissue morphology posed significant obstacles to achieving consistently high performance across all studies. Despite these challenges, the results highlight the potential of advanced AI techniques in enhancing the accuracy and efficiency of CIN2 detection.

6. Artificial Intelligence and Histology in Cervical Cancer Screening

AI and DL are emerging as transformative tools in the field of pathology, particularly regarding the diagnosis of HPV-related cervical lesions. Cervical cancer remains a significant global health burden, with HPV infection recognized as a primary risk factor for its development [40]. Traditional methods of cytological and histological analysis rely heavily on the expertise of pathologists, which can be subject to inter-observer variability and limitations in accuracy. However, with the advent of AI and deep learning technologies, a paradigm shift in how these lesions are diagnosed and managed might happen in the very near future. In fact, with the growing advancement of AI and DL techniques, an increasing number of computer-aided diagnosis methods have been applied in cervical cytology screening due to its high-performance results [74–77]. Since 2016, the use of DL for cervical cytology screening has notably increased. Specifically, the object detection task has made significant advances since 2018, whereas the task of whole slide image (WSI) analysis, which began in 2021, has recently demonstrated remarkable development [5].

Nowadays, thanks to the improvement of digital techniques and imaging equipment, Pap test samples can be transformed into digital slides via scanners to allow for pathological examination. The digitalization of glass slides into WSIs might greatly reduce pathologists' workload while also improving the diagnostic efficiency compared to visual observation at the microscope [4,78].

In the realm of cervical cytology, AI-powered technologies may revolutionize screening programs by enabling automated analysis of Pap test samples. These systems could efficiently triage cases, prioritizing those that require further and urgent review by expert pathologists while expediting the processing of negative samples. Moreover, AI algorithms can accurately classify abnormal cells according to their degree of dysplasia or malignancy, aiding in risk stratification and clinical decision making [5].

One of the key advantages of AI in cervical lesion diagnosis lies in its ability to analyze vast amounts of digital data with speed and consistency. DL algorithms, trained on large datasets of annotated images, can recognize complex patterns and subtle morphological features indicative of HPV infection and associated pre-neoplastic and/or neoplastic lesions. These algorithms can identify abnormal cells with a high level of precision. By leveraging deep neural networks, AI systems can learn from a diverse array of examples, continuously improving their performance and adaptability over time. Moreover, by assisting in the early detection of cervical lesions, AI may also have the potential to reduce the incidence of advanced-stage cervical cancer and improve patient outcomes. Different AI techniques, such as Convolutional Neural Networks (CNNs), Support Vector Machines (SVMs), Recurrent Neural Networks (RNNs), Long-short Term Memory (LSTM), and Gated Recurrent Units (GRUs), each offer unique advantages depending on the task. CNNs are particularly well-suited for image analysis and detection in the early detection of cervical cancer. As deep learning models designed to process image data, CNNs excel at identifying patterns and features in medical images, such as Pap smear slides and colposcopy images. Unlike traditional algorithms, CNNs can detect subtle visual cues that may be missed by human eyes, making them highly effective for tasks like identifying suspect precancerous areas. By contrast, traditional SVMs may struggle with the complexity of medical images, as they perform best with structured, lower-dimensional data. However, SVMs can still be valuable in simpler classification tasks where image resolution and features are well-defined. In addition, for predicting individual risk levels based on HPV test data and patient history, SVMs and Random Forests often outperform CNNs. These models are designed to work well with structured datasets, such as demographic information, test results, and medical history. SVMs, in particular, are effective when the data contain clear boundaries between classes (e.g., high-risk vs. low-risk patients). Random Forests are also well-suited for this task, as they can handle non-linear relationships within the data and provide insight into which factors (e.g., age, HPV strain) are most predictive of risk. CNNs, being more complex and resource-intensive, are not typically necessary for such tabular data. Furthermore, in remote and low-resource settings, CNN-based models used in portable colposcopy devices enable remote diagnosis by analyzing images on site. These models can rapidly provide an initial assessment, allowing non-specialists to take the images, while specialists review them remotely. CNNs are favored here because they excel at processing and analyzing complex image data in real-time, even on lower-powered devices. Other techniques, like SVMs, are less effective for this task due to the high-dimensional, unstructured nature of image data. Additionally, when staging cervical cancer and planning treatment, CNNs again play a central role due to their ability to interpret radiology scans (MRI, CT). CNNs can distinguish different stages of tumors by analyzing the tumor size, shape, and spread in imaging data. Three-dimensional CNNs, an extension of traditional CNNs, are particularly effective in processing volumetric scans, capturing detailed spatial information that is critical for accurate staging. Traditional machine learning models, like SVMs or K-Nearest Neighbors (KNNs), may lack the complexity needed to interpret high-dimensional radiology data.

Lately, the development of new-generation systems of analysis for automated cervical cytology is rapidly improving. Excellent examples of these systems are BestCyte (CellSolutions, Greensboro, NC, USA) [79,80], CytoProcessor (DATEXIM, Caen, France) [81], and Genius Digital Diagnostics System (Hologic, Marlborough, MA, USA) [82]. BestCyte enables remote access through web-based software and comprises a digital scanner and WSI analysis algorithm. CytoProcessor, via machine learning methods, is capable of selecting all suspicious abnormal cells and then displaying them for further review by cytopathologists. CytoProcessor is based on a web application, which allows users to enter in a virtual microscopy-like natural working environment. The Genius Digital Diagnostics System consists of a digital imager, an image management server (IMS), and a review station. This system is based on a novel algorithm of AI and advanced 3D imaging technology, allowing for the detection of abnormal dysplastic or cancerous cells. Moreover, it includes a cloud platform that enables instantaneous linking across laboratories within the same network. To summarize, all three screening systems are based on the use of AI algorithms for primary diagnosis and include platforms for image sharing via web connection. We may assume that the future emerging AI systems for cervical cytology screening will combine and further improve powerful AI (ML/DL-based) analysis algorithms, also providing high-quality imaging devices and easy-to-use viewing software/interface.

In histopathology, AI-driven image analysis has been less developed so far but has the potential to enhance the diagnostic accuracy and efficiency of cervical biopsy interpretation. In the near future, deep learning models may help analyze tissue sections to identify specific histological features associated with HPV infection, such as koilocytosis, dysplasia, and invasive carcinoma. This technology might allow pathologists to make more confident diagnoses, particularly in cases where lesions are subtle or heterogeneous. Furthermore, AI algorithms may facilitate the standardization of diagnostic criteria, ensuring consistency in lesion classification and reporting.

Despite the tremendous promise of AI in cervical lesion diagnosis, several challenges still remain to be addressed. The integration of AI technologies into daily practice requires careful validation and regulatory approval to ensure their safety, effectiveness, and reliability. Additionally, concerns regarding data privacy, algorithm bias, and the interpretability of AI-driven decisions must be addressed to foster trust and acceptance among healthcare providers and patients. Collaborative efforts among researchers, pathologists, industry stakeholders, and regulatory agencies are essential to overcome these challenges and harness the full potential of AI in improving cervical cancer diagnosis.

7. Progression Risk Calculation and Machine Learning

During level II screening, patients who test positive for HPV and require colposcopy are referred to a colposcopist. The management decisions following colposcopy are determined according to established guidelines, which may suggest a biopsy, an excisional procedure, or periodic follow-up based on the specifics of the case. The decision-making process is intricate and must consider a range of variables, including the patient's age, the duration of HPV positivity, cytological grade, histological findings, colposcopic assessment, visualization of the squamocolumnar junction, HPV genotyping, vaccination status, smoking habits, and the presence of recurrent or concurrent co-infections. Recent advancements in understanding HPV-related disease progression have highlighted the importance of integrating additional factors into the risk assessment process [83–87]. Research indicates that individual immune responses, including an evaluation of the vaginal microbiota and the neutrophil-to-lymphocyte ratio, are critical components for more nuanced risk assessment [37,88,89]. These biomarkers can provide insights into the patient's immune status and potential disease progression, which may not be fully captured by traditional assessment methods. Moreover, the integration of artificial intelligence into this process has the potential to significantly enhance risk stratification [90]. AI tools can analyze and weigh a multitude of variables, including HPV genotype, cytological and histological findings, and immune markers, to generate a comprehensive risk score. This score can aid clinicians in determining whether a more interventional approach is needed or if continued monitoring is appropriate. For instance, HPV genotype 16 is associated with a higher risk profile compared to other high-risk HPV types, and this difference in risk should be reflected in the AI-generated risk scores [91]. Incorporating AI into clinical practice requires careful development and validation to ensure accuracy and reliability. Training programs for healthcare professionals should be based on the current literature and best practices to effectively use AI tools in decision-making. AI systems should be designed to account for a variety of risk factors and apply appropriate weights to each, thereby enhancing personalized patient management strategies [19,92,93]. The potential benefits of AI in this context include more precise risk assessments, improved patient outcomes, and a more efficient use of healthcare resources. As research continues to evolve, ongoing updates to AI tools and guidelines will be essential to incorporate new findings and maintain best practices in the management of HPV-related diseases [92]. Despite the transformative potential of AI in healthcare, practical integration faces several limitations. The high cost of AI tools, usually proprietary and under copyright and limitations, make them inaccessible for many smaller facilities with limited budgets. The low standardization of healthcare informatics systems may also play a role in the diffusion of AI systems for compatibility issues when trying to implement new AI technologies. Clinicians who are accustomed to traditional methods may find it challenging to incorporate complex AI-driven models into their daily workflow. This hesitance is partly due to the "black box" nature of many AI algorithms, which seem to provide predictions without clear explanations, making healthcare providers cautious about trusting and acting on them. Another important limitation is the potential privacy issues linked to national law. Overall, these limitations—cost, compatibility, and interpretability—suggest that while AI holds promise, achieving effective and widespread clinical adoption will require addressing these structural, technical, and cultural challenges.

8. Strengths and Limitations

To the best of our knowledge, this is the first review of this scope carried out by a multidisciplinary team of professionals from different fields of expertise (gynecological, histopathological, and computer science). In addition, for this research, we specifically chose articles that deal with histopathological aspects and the potential clinical application of AI. Furthermore, the future potential of artificial intelligence is proposed, such as that of structuring software for the personalization of treatment, which can give rise to new studies and pilot projects. Despite this contribution, the review presents some limitations, which may be inherent to the topic covered but are, above all, specific to AI. In the latter case, these limitations can have a dual nature, both structural (for example, linked to the type/formation of the software or even to the quality of the images) and interpretative. These challenges are due either to the quantity and specificity of the data to be analyzed or to the inability of the machine to distinguish the pathognomonic characteristics of a specific lesion compared to other similar ones, perhaps of a reactive type. In this specific case, one of the intrinsic limitations of our review is the limited number of articles dealing with this topic, especially relating to colposcopy. This is, in fact, a niche sector. Moreover, the results of the different learning algorithms were not compared due to a lack of uniformity in the outcomes reported, with some studies reporting only accuracy and others reporting sensitivity and specificity. This is a problem known to professionals; in fact, it is known that we are very often faced with digital data that are not useful for algorithmic analyses. Indeed, a large volume of information does not automatically correspond to better quality of the resulting applications. Simple data are also useless if not adequately selected and correctly interpreted [94], demonstrating that it is not the technologies that are decisive but the ability to extract value from their use. A further limitation of the proposed analysis concerns the non-homogeneity of the data used together with colposcopic images to predict the presence of cancer. It is well known that the patient's age, the presence of relapse, smoking status, substance dependence, promiscuous behaviors, and other variables related to the patient's health status or behaviors or menstrual phase can have a major influence on the interpretation of colposcopic images and, consequently, on the diagnosis. On the other hand, the papers analyzed are mostly focused on techniques for image classification or the identification of areas for histological sampling, while details on additional parameters, if any, are few and uneven, preventing an accurate comparison among the different techniques analyzed and limiting the reproducibility and verification possibilities of the techniques described. The analyzed articles have also paid little attention to the explainability aspects related to the adopted AI techniques (referred to as "eXplanable AI", or XAI, in the relevant literature). This problem could be partially solved if so-called real-world data, such as registries or electronic health records, were always available. The union of such data is not only fundamental in the panorama of personalized care but, as is known, can improve the predictive power of rehospitalization of some patients [95], thus having an impact not only on the management of the disease but also on the costs and on the diversity of the healthcare system, which can also represent a social barrier [95]. Nonetheless, the use of big data still has limitations inherent in its very nature, such as risks of bias in the selection and collection of the sample (false positives and false negatives), or in the processing of information, which can alter the results. Validation by external sources would, therefore, be desirable to avoid reaching erroneous conclusions [96]. Also connected to this area are the possible problems inherent to the attribution of responsibility in the event of medical errors, which are intertwined with the methodological biases mentioned above and with the protection of privacy and the security of personal data. Another limitation of the literature research is also the lack of information about the generalizability of the proposed approaches. In the articles identified, in fact, the samples analyzed are small and unrepresentative of the extreme variety of situations detectable in clinical practice, both in terms of the heterogeneity among patients' conditions, differences in the clinical instrumentation available to colposcopists, different levels of preparation, and different ways of administering colposcopic examination by medical and/or paramedical personnel in the field. We must also address the limits of medicine relating to the gray areas inherent in our knowledge of problems, such as that of HPV. While HPV screening tests are carried out, despite representing the "gold standard" and multiple or new generations, they are also subject to the risk of interpretative uncertainty. Depending on the choice of what to use to train the algorithm, the accuracy levels can be different. All this also generates a certain distrust toward the use of systems based on artificial intelligence, which can represent a limit to their adoption.

9. Conclusions

AI is rapidly transforming the medical field, with significant advancements in diagnostic and therapeutic practices. In colposcopy, AI demonstrates remarkable potential to enhance the accuracy and efficiency of cervical cancer screening programs. The digitalization of both gynecological and histopathological equipment is a key factor in this progress, facilitating the generation of high-quality images that can be utilized by advanced diagnostic and therapeutic software. This technological evolution presents a cutting-edge approach to improving cervical cancer screening, promising more precise and personalized patient care. The future applications of AI in medicine are extensive. In radiology, AI algorithms are already making strides in analyzing imaging data, aiding in the early detection of diseases. In endoscopy, AI can assist in real-time decision making, while robotic microsurgery benefits from AI's ability to enhance precision and control. Moreover, AI's potential to revolutionize personalized medicine, preventive care, and continuous health monitoring through wearable technology underscores its transformative power across various medical domains. One of the main advantages of AI, which could revolutionize the field of cervical screening, is the ability of its tools to analyze variables of different nature in order to integrate them to generate risk scores. This aspect has a dual potential: both prognostic, since it provides the clinician with the possibility of predicting the progress of the disease or the response to treatment, and research, since it has the potential to identify and select new biomarkers, which, to date, rather than being unknown, remain hidden from "older generation analyses". This represents the largest field of research that will need to be investigated in the future.

Despite the promising prospects, the integration of AI into clinical practice raises several critical considerations. While it has the potential to significantly improve the accuracy of cervical cancer screening and other diagnostic procedures, it is essential to recognize the limitations and challenges associated with its implementation. The expertise of gynecologists and pathologists remains indispensable, as their ultra-specialist skills are crucial for interpreting results and making nuanced clinical decisions. Additionally, AI algorithms are trained on data that may contain biases or errors, which can lead to inaccurate results. This underscores the importance of ongoing research to refine AI systems and ensure that they are based on comprehensive, unbiased data. It is vital to approach AI not as a replacement for clinicians, but as a complementary tool designed to support and enhance clinical practice. The goal should be to provide clinicians with advanced tools that facilitate safer, more targeted, and personalized diagnostic and therapeutic pathways. In conclusion, while AI holds transformative potential for improving diagnostic accuracy and patient outcomes, it is crucial to address the associated challenges with thoughtful consideration. Ensuring transparency, mitigating biases, and integrating AI in a supportive role rather than as a replacement for human expertise will be essential. As technology continues to advance, the collaborative efforts of technologists, clinicians, and researchers will be pivotal in harnessing AI's benefits while upholding the integrity of clinical practice and patient care.

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Glossary

AI (Artificial Intelligence)	A field of computer science focused on creating systems that can perform tasks usually requiring human intelligence, such as learning, problem-solving, and pattern recognition.
CNN (Convolutional Neural Network)	A type of deep learning model especially effective for image-processing tasks. CNNs use convolutional layers to capture spatial features in images, making them suitable for medical imaging analysis.
SVM (Support Vector Machine)	A supervised machine learning algorithm that works well for binary classification tasks, particularly when the data have clear boundaries. SVMs are often used for structured data, like patient information, rather than image data.
Random Forest	An ensemble learning technique that builds multiple decision trees and combines their outputs. Random Forests are known for their accuracy and interpretability, especially in tasks involving tabular data with many variables, like patient histories.
Gradient Boosting Machines (GBMs)	An ensemble method that builds models sequentially to correct previous errors. GBMs are particularly effective for complex tabular data, where they can capture non-linear relationships among variables.
3D CNN	A variation of CNNs that extends to three dimensions, allowing for volumetric data processing. Three-dimensional CNNs are commonly used in analyzing MRI and CT scans where the spatial relationships across slices are important.

RNN (Recurrent Neural Network)	A type of neural network designed to handle sequential data, like time-series information. RNNs can be useful in medical applications where patient data need to be tracked over time.
Predictive Modeling	The use of machine learning models to predict outcomes based on historical data. Predictive models in cervical cancer can forecast treatment responses and survival rates.
Personalized Treatment	Tailoring medical treatment to the individual patient's characteristics, such as their genetic makeup, health history, and specific type of cancer. AI helps personalize treatment by predicting likely outcomes based on these factors.
Deep Learning	A subset of machine learning that involves neural networks with many layers. Deep learning is particularly powerful for image and speech recognition tasks and is widely used in healthcare for analyzing medical images.
Feature Extraction	The process of transforming raw data (like images) into a structured format for analysis. In image processing, features might include shapes, colors, or textures that help AI models detect abnormalities.
Ensemble Learning	A technique where multiple models are combined to improve accuracy. Random Forests and GBMs are examples of ensemble methods, often used in complex medical datasets.
Supervised Learning	A type of machine learning where models are trained on labeled data, meaning each input is associated with a known output. Supervised learning is widely used in healthcare, where data often include both patient information and diagnoses.
Unstructured Data	Data that do not have a predefined format, such as images, text, or audio. CNNs are commonly applied to unstructured data, as they can process images without needing structured inputs.

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