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REVIEW ARTICLE

Advancement in Deep Learning Methods for Diagnosis and Prognosis of Cervical Cancer

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Abstract: Cervical cancer is the leading cause of death in women, mainly in developing countries, including India. Recent advancements in technologies could allow for more rapid, cost-effective, and sensitive screening and treatment measures for cervical cancer. To this end, deep learning-based methods have received importance for classifying cervical cancer patients into different risk groups. Furthermore, deep learning models are now available to study the progression and treatment of cancerous cervical conditions. Undoubtedly, deep learning methods can enhance our knowledge toward a better understanding of cervical cancer progression. However, it is essential to thoroughly validate the deep learning-based models before they can be implicated in everyday clinical practice. This work reviews recent development in deep learning approaches employed in cervical cancer diagnosis and prognosis. Further, we provide an overview of recent methods and databases leveraging these new approaches for cervical cancer risk prediction and patient outcomes. Finally, we conclude the state-of-the-art approaches for future research opportunities in this domain.

Keywords: Deep learning, cervical cancer, diagnosis, neural networks, risk prediction, sensitive screening.

1. INTRODUCTION

Cervical cancer is the fourth most common cancer in women globally. In 2018, an estimated 570,000 women were diagnosed with cervical cancer worldwide, and about 311,000 deaths in women were reported due to cervical cancer [1]. Cervical cancer occurs due to the integration of an extremely common human papillomaviruses (HPV) in the host genome. Almost 99% of cervical cancer cases are linked to infection with high-risk HPV transmitted through sexual contact [2]. Cervical cancer's carcinogenesis process is associated with the expression of viral oncogenic proteins E6 and E7. These proteins can inactivate p53 and pRb, which induces proliferation of continuous cells with increased risk of accumulation of damage of DNA that eventually leads to cervical cancer. The process by which a test is performed to check the existence of abnormal tissues or cancerous cells in the cervix is cervical cancer screening [3]. Cervical Intraepithelial Neoplasia (CIN) detection by cervical cancer screening indicates an abnormal change in the cervix. Physicians rely on different screening methods to differentiate between various types of CIN to decide if patients need treatment or not [4]. Digital cervicography takes cervix photographs after applying 5% acetic acid. Hence automated detection and classification can be used on cervigrams. In object detection and classification, impressive effectiveness has been shown by deep learning models [5, 6].

With the advent of recent technologies, a bulk of multi-omics data on cervical cancer has been available to the research community. Early detection of cervical cancer has become highly important for the efficient management of patients clinically. One of the crucial challenges is transforming biological data into valuable knowledge. To this end, deep learning has recently emerged as a helpful tool that encompasses the power of parallel computing. Various techniques, including artificial neural networks, Bayesian networks, support vector machines, and decision trees, have been applied for a long time in cancer research to make accurate decisions based on predictive models (Fig. **1**). Zhong and colleagues illustrated how machine learning could address the rapidly increasing quantity and complexity of data in the field of environmental science and engineering [7]. In another work, Raza and colleagues used machine learning to predict and rationalize carbon-fluorine bond dissociation energies in an attempt to ease their removal and provide a means for efficient treatment [8]. Using a variety of machine learning algorithms, including feed-forward neural networks, these authors were able to obtain extremely accurate predictions for carbon-fluorine bond dissociation energies. These studies suggest that machine learning could be poten-

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tially exploited as a complementary approach to shed mechanistic insights to guide experimental work. In the past, some researchers have used different techniques in order to screen for cervical cancer at an early stage [9]. Recently, deep learning models have become a popular tool for cancer research. These methods can identify patterns and complex relationships from available multimodal datasets for an effective prognosis of cervical cancer. Considering a significant increase in demand for personalized medicine and the growing developments in deep learning techniques, we hereby review advancements in modern deep learning methods for cervical cancer diagnosis and prognosis [10].

2. CERVICAL CANCER DATABASES

Several databases are now available on cervical cancer, allowing the development of better methods for their early diagnosis and prognosis (Table **1**) [11]. This provides an opportunity for researchers in the domain to design new algorithms to correctly classify cervix types based on available cervical images. Most of these cervix data are obtained from healthy individuals (non-cancerous). Cervical cancer can be successfully treated if diagnosed at an early stage. This decision is critical for the patient and very important for the healthcare provider. The region where cervical cells are most likely to turn cancerous is referred to as the transformation zone. The transformation zone identification is a difficult activity for healthcare providers. Thus, computational-aided decisions can significantly improve the quality and efficiency of cervical cancer screening for patients.

In cancer, risk classification can be challenging as in some women, the virus survives for years, ultimately causing cervical cells to become cancer cells. Therefore, chances of cervical cancer can be significantly reduced by following screening tests as well as taking vaccination for HPV. In addition, electronic health record data from hospitals are used to evaluate cervical cancer screening. Hence, the data focuses on identifying and creating a model to identify the risk factors associated with cervical cancer [12].

Importantly, establishing a fully functional information system would be highly beneficial in successful monitoring and evaluating cervical cancer. In this regard, it would be desirable to link information across the regional or national databases to allow data aggregation on crucial factors for follow-up of cervical cancer progression. Cervical cancer occurs in the region found in the women's health part of the sexual and reproductive health section. All factors found in this particular region include a proper definition, data requirements, data source(s), purpose, and issues [13].

3. DEEP LEARNING ARCHITECTURES

Machine learning algorithms have been widely used to extract relevant information from exponentially growing data. Deep learning is a subset of machine learning where artificial neural networks (Fig. **2**), algorithms inspired by the human brain, learn from large amounts of data. The deep learning architecture is expected to generate more accurate output than traditional machine learning algorithms (Fig. **3**). Deep learning applications involve sequencing data, image recognition, speech recognition, and Natural Language Processing (NLP). There are different deep learning architectures, including Deep Neural Networks (DNNs), Convolutional Neural Networks (CNNs), and Recurrent Neural Networks (RNNs). In bioinformatics, deep learning has vast applications such as imputation, protein structure folding, motif identification, and gene finding. These techniques have

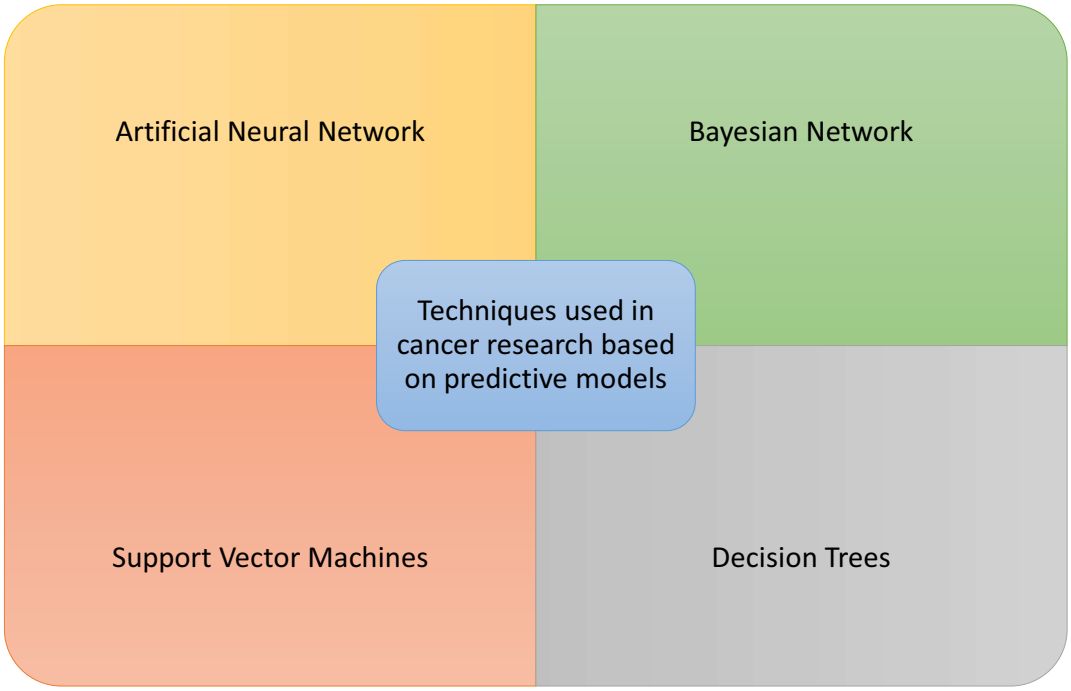

Fig. (1). Various types of techniques used for the prediction of cancer. Artificial Intelligence is widely used in the prognosis of cancer. These four techniques are supervised learning methods that are most commonly used to detect different types of cancer with high accuracy.

Table 1. List of important cervical cancer databases.

Database	Data Type	Description	References (PMID)
Cervical Cancer gene DataBase (CCDB)	Genes	A manually curated catalogue of experimentally validated genes thought to be involved in the different stages of cervical carcinogenesis. Each entry contains information about the gene and protein sequences, their location, architecture, function, chromosomal positions, accession numbers, gene, coding sequence sizes, gene ontology, and homology to other eukaryotic genomes.	21045064 [14]
Danish Database for Cervical Cancer Screening	Cervical cell samples	Danish national cervical cancer screening program; an annual report is published, including nine quality indicators.	27826216 [15]
dbCerEx	Gene expression data	Gene expression data from cervical cancer samples. It includes the genome-wide expression profiles of cervical cancer samples and a web utility to cluster genes with similar expression patterns.	24918550 [16]

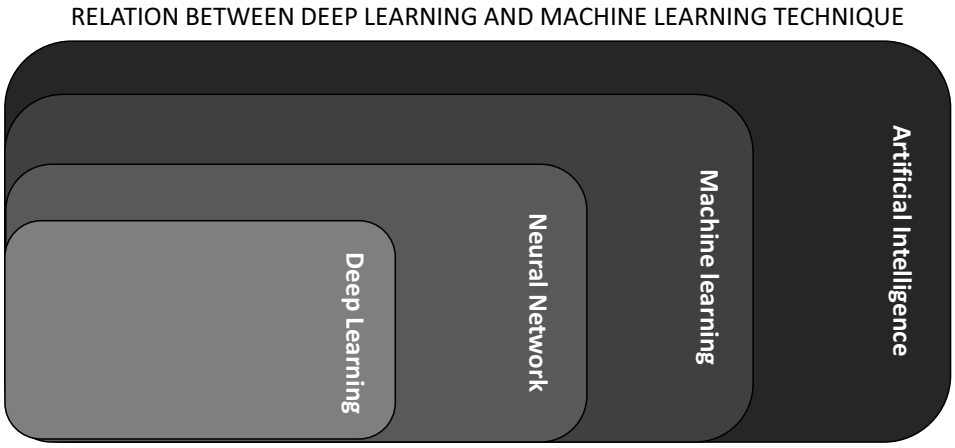

Fig. (2). Relation between deep learning and machine learning techniques. In this image, artificial intelligence can be considered as the universal set with subsets - machine learning followed by neural networks and, lastly, by deep learning. Deep learning is a small niche in machine learning and is a highly specialized technique used to solve complex problems.

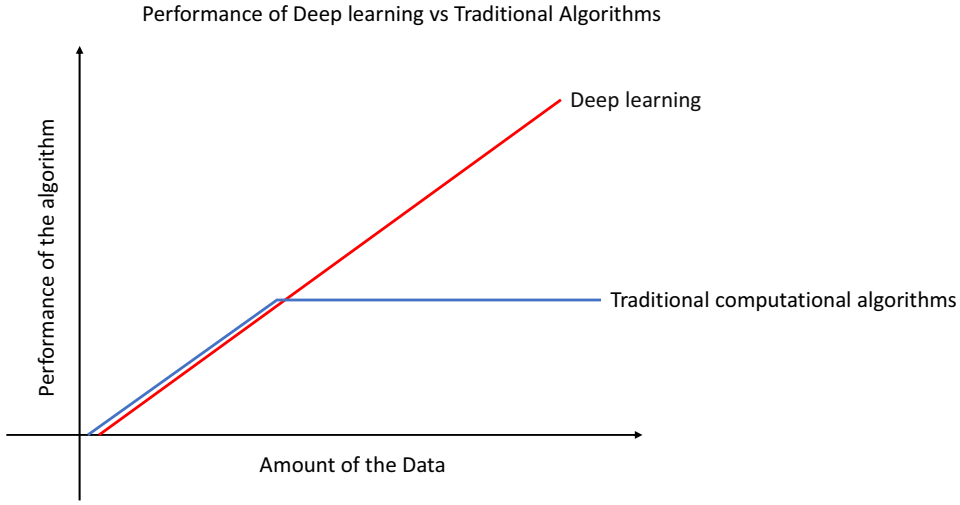

Fig. (3). Performance of deep learning *vs*. traditional algorithms. As seen in the image, deep learning algorithms outperform traditional algorithms as the dataset becomes larger. Deep learning is hence preferred in cancer research as the amount of data is tremendous, and accuracy is to be maximized. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

immense applications in the biological research domains for industry and academia alike. For instance, Google Health has achieved great success in collaboration with DeepMind to develop effective healthcare technologies. Deep learning algorithms use training datasets, similar to most machine learning algorithms, to recognize underlying patterns or to build predictive models. Several algorithms such as Random Forests, Support Vector Machines, Hidden Markov Models, Gaussian networks, and Bayesian networks have been applied extensively in multi-omics and system biology [9, 17].

Deep learning approaches allow solving complex problems using datasets that might be diverse, unstructured, and inter-connected. The human brain is the most complex system. It has the potential to execute trillions of calculations in a brief period. Therefore, neural networks have been developed to mimic the neurons in the brain. We use a machine to run these neural networks to identify patterns, classify objects and perform complex computations on large amounts of data. A neural network consists of three main layers – the input layer, the hidden layers, and the output layers [18]. Various deep learning architectures are described in the following sections.

4. DEEP NEURAL NETWORK (DNN)

The basic structure of DNN consists of three components referred to as input layer, multiple hidden layers, and output layers (Fig. **4**). In DNN, input data is passed to the network, and the output is computed successively at each of the hidden network layers. Each unit's input and weight vectors are multiplied to produce output values of each unit in the successive layer. Deep neural networks can be classified as Multilayer Perceptron (MLP), Sparse Autoencoder (SAE), or Deep Belief Network (DBN) based on the type of layers used in deep neural networks. Among these, MLPs have similar structures as that of neural networks, albeit they contain a more stacked layer. In MLP, the training is executed in two phases, namely, unsupervised pre-training and supervised fine-tuning. On the other hand, SAE and DBN use unlabelled data and also overcome the problem of model overfitting. Over the past few years, DNNs have been widely used in gene expression regulation and protein structure prediction research [19].

5. CONVOLUTIONAL NEURAL NETWORK (CNN)

The basic structure of CNN consists of convolution layers, non-linear layers, and pooling layers (Fig. **5**). The computation of the convolution between local patches and the weight vectors called filters results in forming a group of locally weighted sums called feature maps. This phenomenon occurs due to the processing of highly correlated subregions in data. CNNs are deep learning architectures owing to the analysis of spatial information. Hence, CNNs bear a high success rate in domains including biomedical signal processing and multi-omics. CNNs are applied in the one-dimension grid for genomic sequence motifs, while it is applied in the two-dimension grid for interactions between frequency matrices of biomedical signals and omics data [20].

6. RECURRENT NEURAL NETWORK (RNN)

RNNs are designed to most effectively utilize the information in a sequential manner. RNN and CNN have become popular architectures due to accelerated data acquisition of dynamic Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI). Successes in Natural Language Processing (NLP) have resulted in the application of RNN in the area of biomedical text mining. Attention mechanisms can significantly boost performance and ensure the extraction of more relevant information from the text data. The working of an RNN follows a pattern wherein the information is cycled through a loop. Due to the presence of its internal memory, it considers not only the current input but

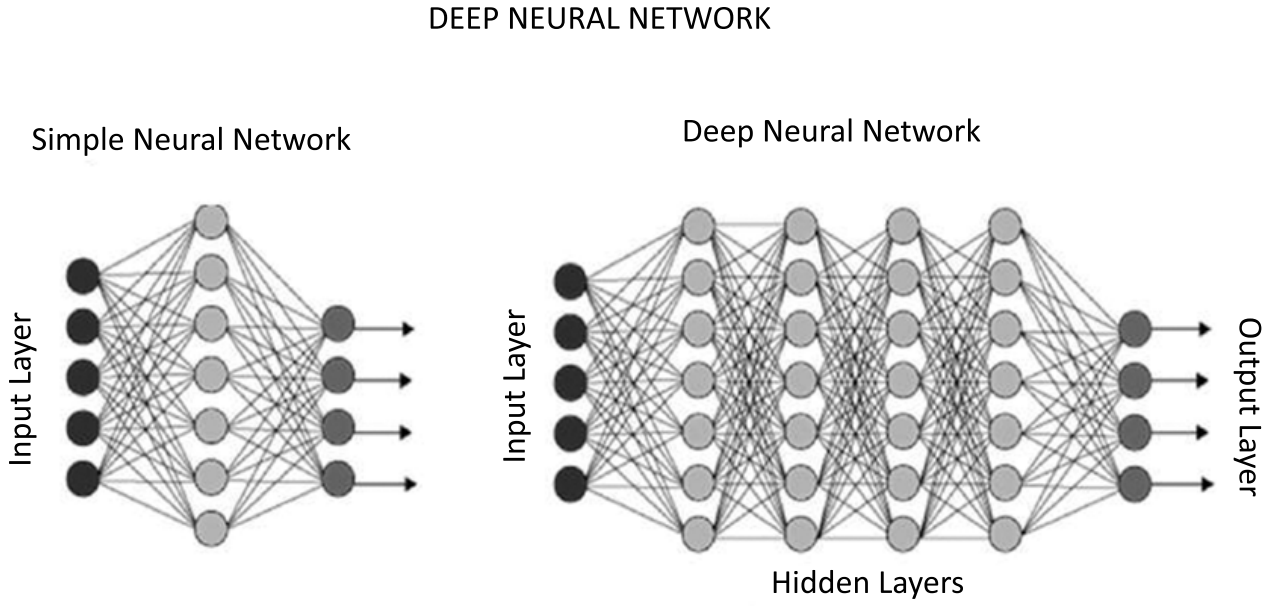

Fig. (4). A simple representation of a deep neural network. A deep neural network is composed of several hidden layers as compared to a simple network. These hidden layers are mathematical functions that convert the input into the desired output, which is a continuous process as the data passes through each layer.

also the previous input which it had received in the earlier stage. Most of the other algorithms only consider the real-time input with no consideration of the input entered in the past. This is where RNNs have an edge. Even though they were developed in the 80s, the advent of technology led to increasing computational power has increased their importance. An RNN generally has short-term memory, which can be boosted by using it in combination with LSTMs. It is hence well suited to analyze and predict sequential data. In the prediction of cervical cancer, several pictures can be analyzed and used to train the model for the prediction of anomalies (Figs. **6** and **7**) [21].

7. NEW DEEP LEARNING TECHNIQUES FOR CERVICAL CANCER DIAGNOSIS

Recently, a digital micro holography platform based on DNA has been developed for point-of-care HPV screening with automated readouts leveraging deep learning algorithms. In the presence of high-risk HPV types 16 or 18 DNA, microbeads were designed to bind the DNA targets and form microbead dimers. The holographic signature of these microbeads is measured and analyzed for cervical cancer diagnosis [22].

Park and colleagues compared deep learning and machine learning models in terms of their ability to detect cervical cancer accurately [23]. Specifically, they compared the deep learning model ResNet-50 against machine learning models, including extreme gradient boost, support vector machine, and random forest. Their study found that ResNet-50 could detect cervical cancer through cervicography images more accurately than these three conventional machine learning models. A deep learning pipeline has been proposed to detect cervix regions and classify cervical tumors (Fig. **8**) [24]. This deep learning pipeline is reported for the first time, with no human intervention required to diagnose the presence of cervical cancer. The most important components of the proposed deep learning pipeline are cervix detection and cervical RoI extraction, RoI processing and data augmentation, automatic feature extraction, and cervical tumor classification [25].

Some researchers are using Mask R-CNN to analyze the nucleus of the cervical cell to identify normal and abnormal nuclear features [26]. The dataset used in this approach comprises liquid-based histological slides obtained from the clinic. A vital attribute of these slides was that they contained cervical cells and various other components, such as white blood cells that mimicked actual clinical settings. The results of this study were promising as the algorithm used achieved per image sensitivity of 91.7%, specificity of 91.7%, and an accuracy of 91.7%.

The deep learning framework is designed for cervical dysplasia diagnosis by using multimodal datasets. The CNN is employed to convert the low-level image data into a feature vector fusible with other non-image modalities. The

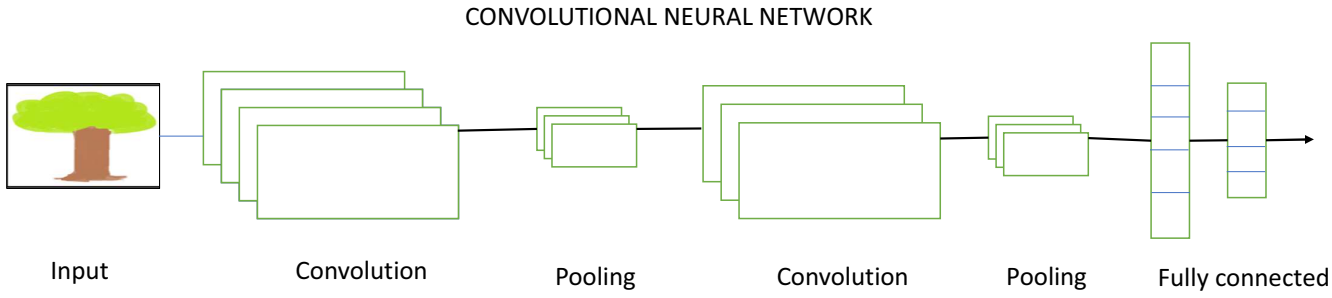

Fig. (5). A simple representation of a convolutional neural network. A CNN uses convolution layers and pooling layers. A convolution is essentially a filter that produces the desired data for the next layer. In other words, it executes a specific function on the data to produce a specific output. The pooling layer enhances the degree of convolutions and acts as an aggregator. It also reduces noise and helps in extracting the required features. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

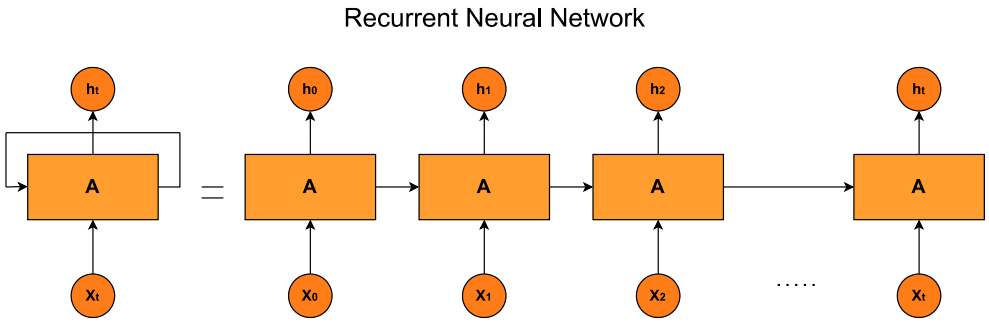

Fig. (6). A simple representation of a recurrent neural network.

non-linear correlations are observed among all the input modalities in a DNN. The multimodal framework is a deep end-to-end network that can learn better complementary features from images and non-image modalities. It automatically gives the final diagnosis for cervical dysplasia with 87.83 % sensitivity at 90 % specificity on a large dataset. This method is shown to significantly outperform methods using a single source of information and also previous multimodal-based tools [27].

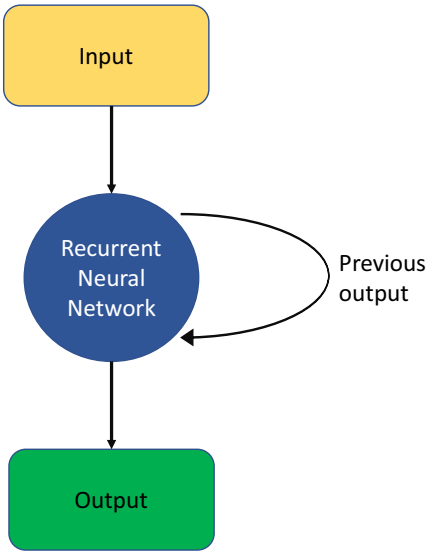

Fig. (7). Principle of a recurrent neural network. The data is continuously refed into the neural network, and this leads to increased learning and higher accuracy.

In recent work, researchers have analyzed p16/Ki-67 dual-stained slides and trained them on biopsy-based gold standards. They used a cloud-based whole-slide imaging platform and a deep learning classifier in this study [28]. In their work, they compared the conventional pap and manual dual-stained slides obtained from three epidemiological studies on cervical and anal pre-cancers of 4,253 patients collated at the Kaiser Permanente Northern California and the University of Oklahoma. Another recent work proposed two CNN architectures to detect cervical cancer using colposcopy images. One of these architectures was the VGG19 (TL) model, and the other was Colposcopy Ensemble Network (CYENET) model [29]. The former is adopted as a transfer learning for the studies in CNN architecture, while the latter classifies cervical cancers using colposcopy images.

Moreover, one recent study demonstrated the importance of the activation functions on the performance of a Residual Network (ResNet) [30]. A deep residual learning-based network was designed to perform cervical cancer screening using a set of 1,070 dynamic T1 contrast-enhanced and 986 T2 weighted imaging MRI images. These images were obtained from 167 early-stage cervical cancer patients [31]. The authors performed a predictive performance evaluation using the receiver operating characteristic curve and confusion matrix analysis. Yu and colleagues developed four classification models in their recent work [32]. The first model was a 10-layer CNN. The second model modified the first model, adding a Spatial Pyramid Pooling (SPP) layer (CNN + SPP) to treat cell images based on their sizes. The third model replaced the CNN layers with the inception module

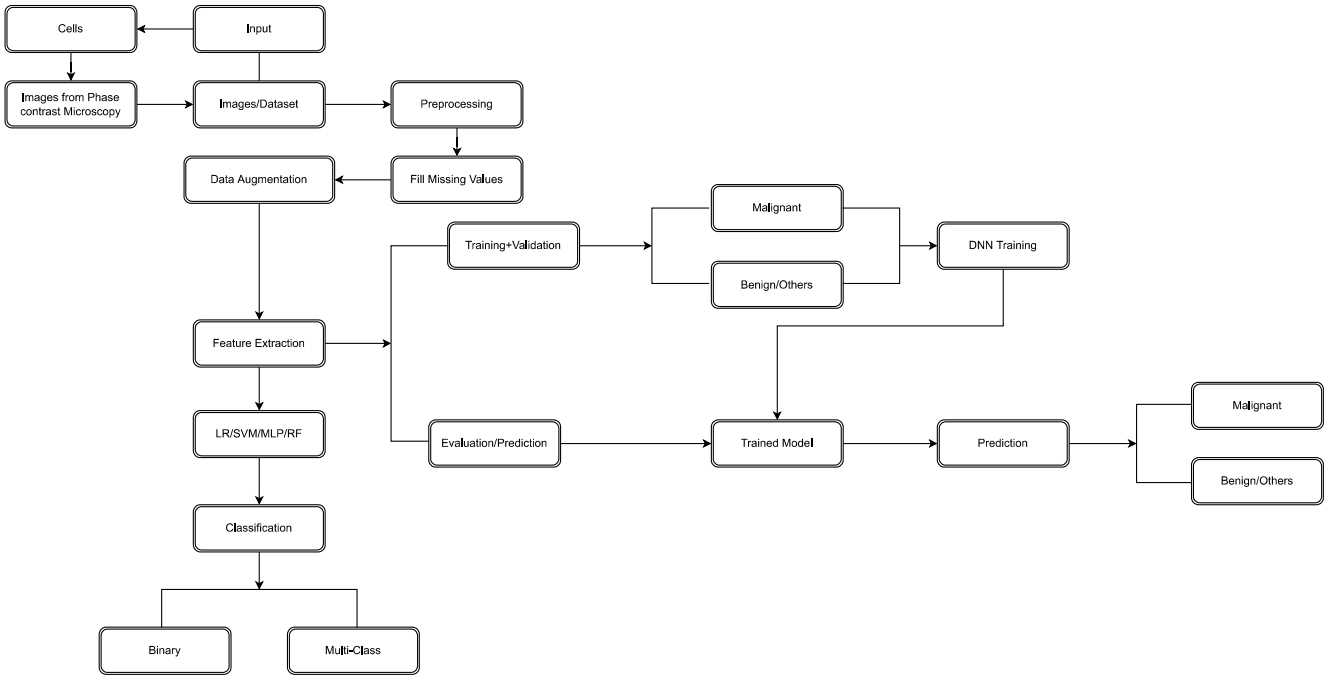

Fig. (8). Pipeline for prediction of cervical cancer using Deep Learning. This is a simple pipeline that utilizes deep learning on image-based datasets (of the cervix) and detects anomalies (tumors). This is a complete pipeline that can be used to train models and detect malignant and benign tumors pertaining to cervical cancer. The DNN training can be specialized as per the requirement, and RNNs, CNNs, R-CNNs, LSTMS, *etc*., can be used for prediction.

(CNN + Inception) based on the first model. However, the fourth model had incorporated both the SPP layer and the inception module into the first model (CNN + inception + SPP). Some authors proposed deep neural networks consisting of three stacked autoencoders with hidden sizes 512, 256, and 128, respectively [33]. In order to perform the classification of pap smear cells, a SoftMax function was used in the outer layer. Some researchers have developed a deep convolutional network that can help pathologists in detecting cervical cancer [34]. They used ThinPreP cytologic test images to train, validate and test their deep learning model. Their model provided an accuracy of 99.4% to distinguish between positive and negative cells. Rahman and colleagues proposed a new framework called DeepCervix to classify cells [35]. They used hybrid deep feature fusion techniques in this model. They compared the accuracy of their model with traditional machine learning techniques such as ResNet-50, late fusion, VGG-16, VGG-19, and XceptionNet. They carried out this comparison across 2-class, 3-class, and 5-class classification on the SIPaKMed dataset, and all were at par or outperformed all traditional techniques in terms of classification accuracy. They also carried out a 7-class classification on the Herlev dataset and achieved an accuracy of 90.32% with their model. Similarly, Mehmood and colleagues developed the CervDetect tool, which uses random forest and Pearson's correlation to select significant features [36]. Their model was found to detect cervical cancer with an accuracy of 93.6%. Table (**2**) summarizes the recent advancement in deep learning techniques focused on cervical cancer research.

8. LIMITATIONS OF DEEP LEARNING

Despite deep learning producing outstanding results, a significant criticism deep learning faces is its use as a "black box." This implies that there is little to no clarity about how deep learning results are obtained internally. In biomedical domains such as cancer research obtaining only the positive outcomes has not been solely the main objective. In particular, cervical cancer is a deadly disease that governs a women's health. Therefore, it necessitates the logical reasoning behind the function of this "black box" before leveraging them for day-to-day clinical practices. The major drawback of deep learning models is the requirement of training data usually lacking in the biological domain. Transfer learning might be used to partly overcome this issue by performing retraining of the data obtained from a huge dataset on the current small dataset. However, this can lead to inaccuracies as different models can predict well on certain data types and be more accurate than the other models [37].

Most of the deep learning algorithms currently used assume the availability of adequate and balanced data for model training. This is generally not the case for the data found in the biomedical domain. The data is often erratic and sometimes limited. Due to these instances, limitations are seen in the processing of raw data dependent on hand-designed features. However, representation learning has the potential to transition from hand-designed to data-driven features. Using multiple non-linear layers in deep learning architectures, it is feasible to obtain hierarchical representations of data with increasing abstraction levels. DNN refers to multilayer perceptrons, stacked autoencoders, deep belief networks, autoencoders, and restricted Boltzmann machines. CNN architecture is mainly seen in image recognition and consists of convolutional layers, non-linear layers, and pooling layers. RNN has been designed to leverage the sequential data information as input with cyclic connectivity among building blocks. For instance, multi-dimensional recurrent neural networks, convolutional autoencoders, and perceptron deep spatiotemporal neural networks are popular building blocks used in RNN [19].

The analysis of internal correlations in high-dimensional data is best performed through DNNs. However, for the analysis of spatial information, CNNs are most suitable. In the coming years, cervical cancer research is bound to benefit immensely from these deep learning approaches due to the exponential assimilation of data in different domains. This data is available in various forms such as images, signals, multi-omics, and electronic medical records. A big chunk of the input data in this domain is usually image-based. For this purpose, a combination of RNN and CNN integrated with attention models is frequently applied in video summarization, image captioning, and image question answering. In cervical cancer, complex dataset acquisition is an expensive process, which tends to limit the size of the data sets. As a result, there are inevitably fewer data from treatment groups than from healthy groups. The usage of human-designed features as input data can be considered to have great benefits in this context [17].

9. FUTURE WORK OPPORTUNITIES

In bioinformatics, deep learning has the huge potential to produce outcomes with higher efficiency compared to traditional machine learning algorithms. However, deep learning methods require further study for enhanced capabilities, multi-modality, and acceleration [17]. This review provided exposure to state-of-the-art established deep learning architectures applied to cervical cancer in terms of input data and research objectives. We have discussed several research-based cervical cancer databases of omics, image, and signal data. Moreover, we provide a comprehensive view of the underlying limitations of these techniques, along with some promising avenues for future research in this domain.

The immense potential that the application of deep learning algorithms carries in the biomedical domain has caught the attention of the scientific community for a long time. The ongoing research work in deep learning mainly focuses on three categories, namely, advanced optimization algorithms, parallel and distributed computing, and specialized hardware and software. To this end, further developments in parallel and distributed computing are expected to remarkably speed up the computation time, which is highly sought-after by biomedical researchers [17]. Furthermore, designing deep learning architecture is a promising future trend in this research domain. Many tasks such as algorithm learning, complex question answering, and memory networks can be efficiently solved using LSTMS, RNNs, R-CNNs, or their combinations.

Besides classical supervised and unsupervised learning, the ongoing work on semi-supervised and reinforcement

Table 2. Comparison of various Deep Learning (DL) techniques to predict cervical cancer.

References	Data Type	Approach Used	DL Technique	Results
[23]	4,119 cervicography images.	5-fold cross-validation and Receiver Operating Characteristics (ROC) analysis	ResNet-50, XGB, Support Vector Machine (SVM) and Random Forest (RF)	• AUC: ○ ResNet-50 = 0.97 (CI 95% 0.949–0.976) ○ XGB = 0.82 (CI 95% 0.797–0.851) ○ SVM = 0.84 (CI 95% 0.801–0.854) ○ RF = 0.79 (CI 95% 0.804–0.856)
[28]	68,800 augmented images.	Cloud-based whole-slide imaging platform with a deep-learning classifier.	CNN with four layers and Inception-v3 with 48 layers.	● AI-based DS had lower positivity than cytology (P < .001) and manual DS (P < .001) with equal sensitivity and substantially higher specificity compared with both Pap (P < .001) and manual DS (P < .001), respectively. ● Compared with Pap, AI-based DS reduced referral to colposcopy by one-third (41.9% *vs*. 60.1%, P < .001).
[29]	5679 colposcopy images.	CNN architectures.	CNN-VGG19 (TL) model, Colposcopy Ensemble Network (CYENET).	● Classification accuracy: VGG19 (73.3%), CYENET (92.3%)
[30]	Colposcopy images of healthy and pre-cancerous cervixes.	Three very deep residual learning-based residual networks (18 layers) of the same structure with different activation functions.	CNN with ReLU, Leaky-ReLU, and PReLU activation functions.	● ReLu - ResNet - 98.3% (Maximum number of epochs – 30) ● Leaky - ReLu - ResNet – 99.2% (Maximum number of epochs – 30) ● PReLu - ResNet - 100% (Maximum number of epochs – 30) ● Adam based CNN - 90% (Maximum number of epochs – 50) ● ResNet – 84.10%
[31]	2,056 clinical MRI images (862 vessel invasions and 1,194 non-vessel invasions).	Various deep learning models were used on the data.	CNN-VGGNet, GoogLeNet (Inception-v3), Residual Network (ResNet-v2), and DenseNet .	For the T2WI dataset: ● Adapted VGG16 - 0.607 ● Adapted VGG19 - 0.691 ● AdaptedInception-v3 - 0.600 ● AdaptedResNet50-v2 - 0.605 ● AdaptedDenseNet 121 – 0.612 ● Adapted VGG19-SE - 0.624 ● Adapted VGG19-CBAM - 0.747 For the DCE-T1 dataset: ● Adapted VGG16 - 0.759 ● Adapted VGG19 – 0.768 ● AdaptedInception-v3 - 0.613 ● AdaptedResNet50-v2 - 0.675 ● AdaptedDenseNet 121 – 0.670 ● Adapted VGG19-SE - 0.820 ● Adapted VGG19-CBAM - 0.758
[32]	2504 cell samples (1202 abnormal and 1302 standard samples).	Four CNN-based classification models with different layers were developed.	CNN, CNN with inception module, CNN with SPP layer, CNN with inception module, and SPP layer.	● MODEL A – 92.0 ● MODEL B – 94.8 ● MODEL C – 94.2 ● MODEL D – 98.0

(Table 2) contd….

References	Data Type	Approach Used	DL Technique	Results
[33]	Pap-smear images.	Pap-smear images are analyzed, and cells are classified using a stacked autoencoder-based deep neural network.	DNN with three stacked auto-encoders.	● Average accuracy achieved for 2-class classification among normal and abnormal cells is 98.2% ● Average accuracy achieved 4-class classification among normal, mild, moderate, and severe dysplastic cells is 93.8 % .
[34]	424,106 TCT images.	CNN containing convolution kernel, an activation function, and a pooling function of 3 × 3 and 1 × 1 sizes	CNN	• Sensitivity = 99.4% and • Specificity = 34.8% • AUC = 0.67
[35]	4,049 annotated cervical pap smear cell images.	Hybrid Deep Feature Fusion (HDFF) technique based on DL. The results were analysed for binary class, 3-class and 5-class classification problems.	VGG16, VGG19, ResNet-50, XceptionNet, late fusion (LF) and HDFF.	● Binary Classification: The accuracies of the models are as follows: ○ VGG16 = 99.85 ○ VGG19 = 98.77 ○ ResNet-50 = 99.38 ○ XceptionNet – 98.31 ○ LF = 99.85 ○ HDFF = 99.85 ● 3-Class Classification: The accuracies of the models are as follows: ○ VGG16 = 97.90 ○ VGG19 = 96.18 ○ ResNet-50 = 96.18 ○ XceptionNet = 89.64 ○ LF = 98.52 ○ HDFF = 99.38 ● 5-Class Classification: The accuracies of the models are as follows: ○ VGG16 = 98.27 ○ VGG19 = 96.43 ○ ResNet-50 = 96.06 ○ XceptionNet = 65.77 ○ LF = 98.64 ○ HDFF = 99.14
[36]	Existing patient history, practices, and procedures and demographic statistics for 858 instances with 32 features per scenario.	CervDetect that uses machine learning algorithms to eval-uate the risk elements of malignant cervical formation.	RF and shallow neural networks.	● Accuracy = 93.6% ● Mean squared error = 0.071 ● False-positive rate = 6.4% ● False-negative rate = 100%

(Table 2) contd….

References	Data Type	Approach Used	DL Technique	Results
[38]	518,000 patient's diagnosis records, medications, doctor orders, and laboratory examination.	Two-stage prediction model, RNN-2-DT. Events prediction model using gated recurrent units (GRU) based on recurrent neural network (RNN).	RNN, LSTMS.	1) Model Recall Rates for the RNN-2-DT model under different K values • 77.4%, K=10 (Unstandardized Judgement) • 79.3%, K=20 (Unstandardized Judgement) • 85.6%, K=30 (Unstandardized Judgement) • 86.5%, K=10 (Standardized Judgement) • 88.7%, K=20 (Standardized Judgement) • 90.3%, K=30 (Standardized Judgement) 2) Model MAP values for the RNN-2-DT model under different K values • 58.5%, K=10 (Unstandardized Judgement) • 60.1%, K=20 (Unstandardized Judgement) • 65.6%, K=30 (Unstandardized Judgement) • 61.3%, K=10 (Standardized Judgement) • 68.5%, K=20 (Standardized Judgement) • 70.1%, K=30 (Standardized Judgement)
[39]	Hematoxylin-Eosin (HE) stained histopathological images.	CNN and Long-Short Term Memory (LSTM) by utilizing histopathological pictures.	CNN, LSTM	• Accuracy is 94.96%

Abbreviations: DS - Dual-Stained; CYENET - Colposcopy Ensemble Network; ReLU - Rectified linear activation unit; PReLU - Parametric rectified linear activation unit; ResNet - Residual neural network; GRU - Gated Recurrent Units; SPP - Spatial Pyramid Pooling; CBAM - Convolution Block Attention Module; VGG - Visual Geometry Group; T2WI - T2 weighted imaging; DCE-T1 - Dynamic T1 contrast-enhanced; TCT - ThinPrep Cytologic Test; XGB - Extreme Gradient Boost, LF- Late Fusion, HDFF- Hybrid Deep Feature Fusion; AUC - Area Under the Curve

learning is gaining popularity due to their ability to analyze both labeled and unlabelled data. This provides more versatility to these approaches over classical ones. Reinforcement learning resembles human learning, which has shown great promise for artificial intelligence in healthcare data. For instance, ladder networks used in the recent work can skip connection to traditional MLP or CNNs. Thus, this concurrently reduces the sum of supervised and unsupervised cost functions to denoise representation across different model levels [17].

Despite the huge potential and increased demand, significant challenges exist in the employment of deep learning techniques for cervical cancer research. The major challenges include the availability of limited and heterogeneous data, selection of appropriate deep learning frameworks, and selection of hyperparameters. Most importantly, interpretation and deduction of deep learning results impose a big hurdle. Thus, even though deep learning approaches hold promise, they should not be treated as a silver bullet for ad hoc cancer research applications. The success of deep learning approaches in the diagnosis and prognosis of cervical cancer critically depends on the careful analysis of its limitations and subsequent preparation in order to circumvent them.

CONCLUSION

Cervical cancer is one of the leading causes of death in females worldwide. The successful treatment of cervical cancer heavily relies on a timely diagnosis of the associated symptoms. If cervical cancer can be detected successfully at an earlier stage, the chances of survival are likely to be enhanced. In this review, we described the conventional approaches used for cervical cancer diagnosis along with their limitations. Next, we provided a summary of the various cervical cancer databases that have been made publicly available to the research communities over the last few years. We reviewed in detail the machine learning and, in particular, state-of-the-art deep learning methods that are being employed recently for the diagnosis and prognosis of cervical cancer effectively. We discussed the various architectures and algorithms that can be applied based on the type of data available to predict the onset of cervical cancer. Lastly, we have reviewed some of the limitations of deep learning methods used in this domain. In summary, this review provides valuable insight into ongoing research on the deep learning methods customized for cervical cancer diagnosis and prognosis in the future.

LIST OF ABBREVIATIONS

CIN	=	Cervical Intraepithelial Neoplasia
CNN	=	Convolutional neural network
CT	=	Computed Tomography
DBN	=	Deep Belief Network
DNN	=	Deep neural network
EEG	=	Electroencephalogram
HPV	=	Human Papillomaviruses
LSTM	=	Long Short Term Memory

MLP	=	Multilayer Perceptron
MRI	=	Magnetic Resonance Imaging
PET	=	Positron Emission Tomography
PSSM	=	Position-specific Scoring Matrix
R-CNN	=	Region-Based Convolutional Neural Networks
RNN	=	Recurrent neural network
SAE	=	Sparse Autoencoder

AUTHORS' CONTRIBUTIONS

PY wrote the manuscript; AG and AP prepared the figures; PY designed and supervised the study; all authors contributed to manuscript writing; all authors contributed by comments and approved the final manuscript.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] WHO. Cervical cancer. Available from: https://www.who.int/health-topics/cervical-cancer#tab=tab_1 (Accessed on: 2022 Jan 2).

[2] Burd, E.M. Human papillomavirus and cervical cancer. *Clin. Microbiol. Rev.,* **2003**, *16*(1), 1-17. http://dx.doi.org/10.1128/CMR.16.1.1-17.2003 PMID: 12525422

[3] Yeo-Teh, N.S.L.; Ito, Y.; Jha, S. High-risk human papillomaviral oncogenes E6 and E7 target key cellular pathways to achieve oncogenesis. *Int. J. Mol. Sci.,* **2018**, *19*(6), 1706. http://dx.doi.org/10.3390/ijms19061706 PMID: 29890655

[4] Mello, V. Renee K. *Sundstrom. Cervical Intraepithelial Neoplasia*; StatPearls Publishing: USA, **2021**.

[5] Kim, E.; Huang, X. *A Data Driven Approach to Cervigram Image Analysis and Classification*; Springer Netherlands, **2013**, pp. 1-13. http://dx.doi.org/10.1007/978-94-007-5389-1_1

[6] Magrina, J.F.; Zanagnolo, V.L. Robotic surgery for cervical cancer. *Yonsei Med. J.,* **2008**, *49*(6), 879-885. http://dx.doi.org/10.3349/ymj.2008.49.6.879 PMID: 19108008

[7] Zhong, S.; Zhang, K.; Bagheri, M.; Burken, J.G.; Gu, A.; Li, B. Machine learning: New ideas and tools in environmental science and engineering. *Environ. Sci. Technol.,* **2021**, *2021*, acs.est.1c01339.

[8] Raza, A.; Bardhan, S.; Xu, L.; Yamijala, S.S.R.K.C.; Lian, C.; Kwon, H.; Wong, B.M. A machine learning approach for predicting defluorination of Per- and Polyfluoroalkyl Substances (PFAS) for their efficient treatment and removal. *Environ. Sci. Technol. Lett.,* **2019**, *6*(10), 624-629. http://dx.doi.org/10.1021/acs.estlett.9b00476

[9] Kourou, K.; Exarchos, T.P.; Exarchos, K.P.; Karamouzis, M.V.; Fotiadis, D.I. Machine learning applications in cancer prognosis and prediction. *Comput. Struct. Biotechnol. J.,* **2014**, *13*, 8-17. http://dx.doi.org/10.1016/j.csbj.2014.11.005 PMID: 25750696

[10] Cao, C.; Liu, F.; Tan, H.; Song, D.; Shu, W.; Li, W.; Zhou, Y.; Bo, X.; Xie, Z. Deep learning and its applications in biomedicine. *Genom. Proteom. Bioinf.,* **2018**, *16*(1), 17-32. http://dx.doi.org/10.1016/j.gpb.2017.07.003 PMID: 29522900

[11] Intel & MobileODT. Cervical Cancer Screening. Available from: https://www.kaggle.com/c/intel-mobileodt-cervical-cancer-screening/overview (Accessed on: 2021 Jul 18).

[12] Christian, R. Using data from cervical cancer risk classification. Available from: https://www.kaggle.com/saflynn/cervical-cancer-lynn/data (Accessed on: 2021 Jul 16).

[13] USAID. Cervical cancer, measure evaluation, family planning and reproductive health indicators database. Available from: https://www.data4impactproject.org/prh/womens-health/cervical-cancer/ (Accessed on 2021 Jul 21).

[14] Agarwal, S.M.; Raghav, D.; Singh, H.; Raghava, G.P.S. CCDB: A curated database of genes involved in cervix cancer. *Nucleic Acids Res.,* **2011**, *39*, D975-9. http://dx.doi.org/10.1093/nar/gkq1024

[15] Rygaard, C. The Danish quality database for cervical cancer screening. *Clin. Epidemiol.,* **2016**, *8*, 655-660. http://dx.doi.org/10.2147/CLEP.S99509 PMID: 27826216

[16] Zhou, L.; Zheng, W.; Luo, M.; Feng, J.; Jin, Z.; Wang, Y.; Zhang, D.; Tang, Q.; He, Y. dbCerEx: A web-based database for the analysis of cervical cancer transcriptomes. *PLoS One,* **2014**, *9*(6), e99834. http://dx.doi.org/10.1371/journal.pone.0099834 PMID: 24918550

[17] Min, S.; Lee, B.; Yoon, S. Deep learning in bioinformatics. *Brief. Bioinform.,* **2017**, *18*(5), 851-869. PMID: 27473064

[18] Glattfelder, J.B. *The consciousness of reality*; Springer, **2019**, pp. 515-95. http://dx.doi.org/10.1007/978-3-030-03633-1

[19] Sarker, I.H. Deep learning: A comprehensive overview on techniques, taxonomy, applications and research directions. *SN Comput. Sci.,* **2021**, *2*(6), 420. http://dx.doi.org/10.1007/s42979-021-00815-1 PMID: 34426802

[20] Yamashita, R.; Nishio, M.; Do, R.K.G.; Togashi, K. Convolutional neural networks: An overview and application in radiology. *Insights Imag.,* **2018**, *9*(4), 611-629. http://dx.doi.org/10.1007/s13244-018-0639-9 PMID: 29934920

[21] Salehinejad, H; Sankar, S; Barfett, J; Colak, E; Valaee, S. Recent advances in recurrent neural networks. **2017**.

[22] Pathania, D.; Landeros, C.; Rohrer, L.; D'Agostino, V.; Hong, S.; Degani, I.; Avila-Wallace, M.; Pivovarov, M.; Randall, T.; Weissleder, R.; Lee, H.; Im, H.; Castro, C.M. Point-of-care cervical cancer screening using deep learning-based microholography. *Theranostics,* **2019**, *9*(26), 8438-8447. http://dx.doi.org/10.7150/thno.37187 PMID: 31879529

[23] Park, Y.R.; Kim, Y.J.; Ju, W.; Nam, K.; Kim, S.; Kim, K.G. Comparison of machine and deep learning for the classification of cervical cancer based on cervicography images. *Sci. Rep.,* **2021**, *11*(1), 16143. http://dx.doi.org/10.1038/s41598-021-95748-3 PMID: 34373589

[24] Jusman, Y.; Ng, S.C.; Abu Osman, N.A. Intelligent screening systems for cervical cancer. *Sci. World J.,* **2014**, *2014,* 810368. http://dx.doi.org/10.1155/2014/810368 PMID: 24955419

[25] Alyafeai, Z.; Ghouti, L. A fully-automated deep learning pipeline for cervical cancer classification. *Expert Syst. Appl.,* **2020**, *141,* 112951. http://dx.doi.org/10.1016/j.eswa.2019.112951

[26] Sompawong, N.; Mopan, J.; Pooprasert, P.; Himakhun, W.; Suwannarurk, K.; Ngamvirojcharoen, J. Automated pap smear cervical cancer screening using deep learning. *IEEE Eng. Med. Biol. Soc. Ann. Int. Conf.,* **2019**, *2019*, 7044-8. http://dx.doi.org/10.1109/EMBC.2019.8856369

[27] Xu, T.; Zhang, H.; Huang, X.; Zhang, S.; Metaxas, D.N. Multimodal deep learning for cervical dysplasia diagnosis. **2016**, *2016*, 115-23. http://dx.doi.org/10.1007/978-3-319-46723-8_14

[28] Wentzensen, N.; Lahrmann, B.; Clarke, M.A.; Kinney, W.; Tokugawa, D.; Poitras, N.; Locke, A.; Bartels, L.; Krauthoff, A.; Walker, J.; Zuna, R.; Grewal, K.K.; Goldhoff, P.E.; Kingery, J.D.;

Castle, P.E.; Schiffman, M.; Lorey, T.S.; Grabe, N. Accuracy and efficiency of deep-learning-based automation of dual stain cytology in cervical cancer screening. *J. Natl. Cancer Inst.,* **2021**, *113*(1), 72-79. http://dx.doi.org/10.1093/jnci/djaa066 PMID: 32584382

[29] Chandran, V.; Sumithra, M.G.; Karthick, A.; George, T.; Deivakani, M.; Elakkiya, B.; Subramaniam, U.; Manoharan, S. Diagnosis of cervical cancer based on ensemble deep learning network using colposcopy images. *BioMed Res. Int.,* **2021**, *2021,* 5584004. http://dx.doi.org/10.1155/2021/5584004 PMID: 33997017

[30] Adweb, K.M.A.; Cavus, N.; Sekeroglu, B. Cervical cancer diagnosis using very deep networks over different activation functions. *IEEE Access,* **2021**, *9*, 46612-46625. http://dx.doi.org/10.1109/ACCESS.2021.3067195

[31] Jiang, X.; Li, J.; Kan, Y.; Yu, T.; Chang, S.; Sha, X.; Zheng, H.; Luo, Y.; Wang, S. MRI based radiomics approach with deep learning for prediction of vessel invasion in early-stage cervical cancer. *IEEE/ACM Trans. Comput. Biol. Bioinf.,* **2021**, *18*(3), 995-1002. http://dx.doi.org/10.1109/TCBB.2019.2963867 PMID: 31905143

[32] Yu, S.; Feng, X.; Wang, B.; Dun, H.; Zhang, S.; Zhang, R.; Huang, X. Automatic classification of cervical cells using deep learning method. *IEEE Access,* **2021**, *9*, 32559-32568. http://dx.doi.org/10.1109/ACCESS.2021.3060447

[33] Singh, S.K.; Goyal, A. A stack autoencoders based deep neural network approach for cervical cell classification in pap-smear images. *Recent Adv. Comput. Sci. Commun.,* **2021**, *14*(1), 62-70. http://dx.doi.org/10.2174/1389202920666190313163414

[34] Tan, X.; Li, K.; Zhang, J.; Wang, W.; Wu, B.; Wu, J.; Li, X.; Huang, X. Automatic model for cervical cancer screening based on convolutional neural network: A retrospective, multicohort, multicenter study. *Cancer Cell Int.,* **2021**, *21*(1), 35. http://dx.doi.org/10.1186/s12935-020-01742-6 PMID: 33413391

[35] Rahaman, M.M.; Li, C.; Yao, Y.; Kulwa, F.; Wu, X.; Li, X.; Wang, Q. DeepCervix: A deep learning-based framework for the classification of cervical cells using hybrid deep feature fusion techniques. *Comput. Biol. Med.,* **2021**, *136,* 104649. http://dx.doi.org/10.1016/j.compbiomed.2021.104649 PMID: 34332347

[36] Mehmood, M.; Rizwan, M.; Gregus, M.; Abbas S. Machine learning assisted cervical cancer detection. *Front. Public Health,* **2021**, *2021*, 9.

[37] Manna, A.; Kundu, R.; Kaplun, D.; Sinitca, A.; Sarkar, R. A fuzzy rank-based ensemble of CNN models for classification of cervical cytology. *Sci. Rep.,* **2021**, *11*(1), 14538. http://dx.doi.org/10.1038/s41598-021-93783-8 PMID: 34267261

[38] Yan, Y.; Zhao, K.; Cao, J.; Ma, H. Prediction research of cervical cancer clinical events based on recurrent neural network. *Proc. Comput. Sci.,* **2021**, *183*, 221-229. http://dx.doi.org/10.1016/j.procs.2021.02.052

[39] Sridevi, A.K.; Adhish, P.; Sreeram, M. Cervical cancer detection using Convolutional Neural Network(CNN) and Long-Short Term Memory(LSTM) based on histopathological images. *Ann. Rom. Soc. Cell Biol.,* **2021**, *25*(06), 5875-5883.