Role of Deep Learning in Diagnosis, Treatment, and Prognosis of Oncological Conditions

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Abstracts: Deep learning, a branch of artificial intelligence, excavates massive data sets for patterns and predictions using a machine learning method known as artificial neural networks. Research on the potential applications of deep learning in understanding the intricate biology of cancer has intensified due to its increasing applications among healthcare domains and the accessibility of extensively characterized cancer datasets. Although preliminary findings are encouraging, this is a fast-moving sector where novel insights into deep learning and cancer biology are being discovered. We give a framework for new deep learning methods and their applications in oncology in this review. Our attention was directed towards its applications for DNA methylation, transcriptomic, and genomic data, along with histopathological inferences. We offer insights into how these disparate data sets can be combined for the creation of decision support systems. Specific instances of learning applications in cancer prognosis, diagnosis, and therapy planning are presented. Additionally, the present barriers and difficulties in deep learning applications in the field of precision oncology, such as the dearth of phenotypical data and the requirement for more explicable deep learning techniques have been elaborated. We wrap up by talking about ways to get beyond the existing challenges so that deep learning can be used in healthcare settings in the future.

Keywords: Cancer genomics, Deep Learning, Neural Networks, Transcriptomics, Therapeutic Measures, Prognosis.

1. INTRODUCTION

The goal of artificial intelligence (AI), which is the umbrella term for a variety of technologies, is to computationally imitate human intelligence. Machine learning (ML), a subcategory of artificial intelligence, deals with forecasting by utilizing mathematical algorithms to find patterns in data. Deep learning (DL), a subcategory of ML, is involved in making predictions by using algorithms based on multilayered neural networks in similarity with the brain's neural architecture. In contrast with other ML techniques like logistic regression, DL allows the model to extend exponentially with the increasing data quantity and dimensionality [1]. So, DL was found very useful in solving complicated issues viz, categorization of images at large scale, processing of natural language, recognition of speech, and translation. A revolution is driven by precision health in the field of oncology due to an increase in the availability and integration of various data types such as histopathological data, and genomic and transcriptomic data as mentioned in Fig. 1 [2]. There is a significant role of expertise and time in the analysis and interpretation of such data types for clinical and translational studies. Furthermore, integration of single data type is easier than resource-intensive multifaceted data of a complex nature. It requires algorithmic language-based models which utilize a massive amount of intricated multiple features. The application of ML algorithms is increasing in the field of oncology for early detection, characterization, and control of cancer [3], [4]. The profound understanding and characterization of such complexities and harnessing of multifaceted data types is possible with the DL model [5], [6]. We have elaborated on the role of deep learning in the field of cancer diagnosis, therapeutic measures, and prognosis along with recent advancements. The DL model applications for histopathological and omics data sets of multiple sources have been focused. Further, the applications of DL models in genomic traits evaluation,

histological inferences, microenvironment profiling, survivability prediction, and prognosis in the field of oncology have been elaborated along with their future role in metagenomics, spatial transcriptomics, and pharmacogenomics. The current challenges and potential strategies have been concluded concerning clinical settings.

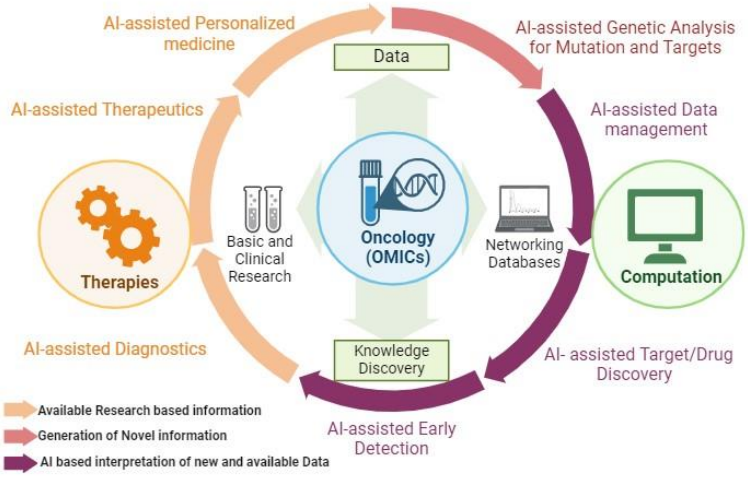

Fig. 1. Role of Artificial Intelligence in Oncology: data base networking is linked with computational strategies while clinical research linked with diagnostics (early detection), and therapeutics (personalized medicine)

1.1. Artificial Neural Network: An Emerging DL Technique

Artificial neural networks are used in deep learning (DL) to extract representative, non-linear, and entangled characteristics from large, high-dimensional data sets [1]. Millions of intricately connected computer neurons arranged into successive layers make up a typical deep neural network. A neuron in each layer is linked to other neurons in the preceding layer (to receive information) and in the succeeding layer (to transmit information). A neural network receives data and sends it to its input layer before sending the information to subsequent layers, which are typically referred to as hidden layers. After that, the data is millions of times multiplied, split, added, and subtracted before reaching the output layer, where it is transformed into a prediction. Each training sample and label pair is fed into a neural network for supervised deep learning, and its weights and thresholds are changed to get the prediction closer to the given label. These training weights and thresholds are frozen and applied to predict unknown (test) data.

2. METHODOLOGY

Several protocols were adhered to in order to guarantee an excellent review of the literature on the role of deep learning techniques in diagnosis, treatment, and prognosis of oncological conditions. A thorough search of the peer-reviewed literature was conducted; dissertations, short papers, reports, editorials, posters, and posters were not included. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were considered. Deep learning, neural networks, oncology, cancer, metastasis, precision oncology, transcriptomics, genomics, prediction and classification were the search terms used to retrieve every article from Web of Science, PubMed, and Google Scholar. Research focused on cancer prediction using deep learning techniques were eligible for inclusion. The papers were evaluated based on their titles, abstracts, and full texts. Fig. 2 highlights the selection process and overall methodology.

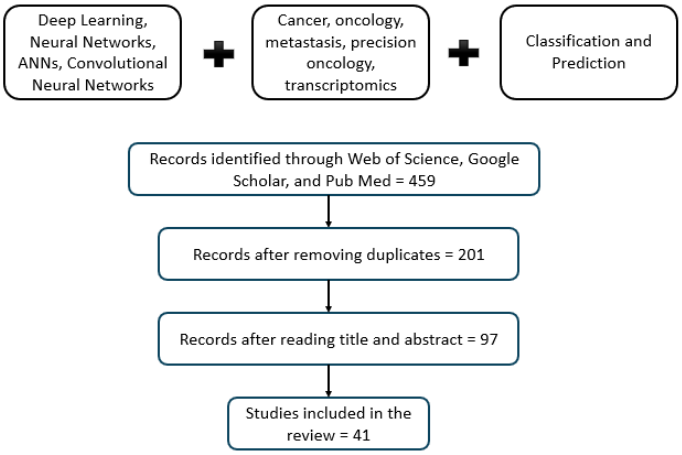

Fig. 2. The step-by-step methodology for the identification, screening, eligibility, and inclusion of articles

3. RESEARCH FINDINGS

The findings from the review of these articles are:

3.1. Role of Deep Learning in Oncology

To improve patient diagnosis, prognosis, and therapy selection, a range of deep learning (DL) techniques that combine histopathological, genomic, or transcriptomic data are used in medical practices and experimental oncology. Oncology still requires human intervention, despite the advent of DL methods. Therefore, the purpose of DL is not to supplant humans but rather to offer assistance with decisions that help clinicians in the clinical care of cancer patients and cancer scientists in their study of the disease [7].

Histopathology and cytopathology are the classic methods used to diagnose cancer. They verify the existence of tumour cells in patient samples, evaluate cancer-related indicators, and describe characteristics such as tumour kind, stage, and grade. This microscopy-based evaluation is essential, but it takes a lot of work and is a little subjective [8], [9]. Millions of minute cellular characteristics can be seen in a histopathological image magnified at a high level of magnification (usually 20x or 40x), and deep CNN models excel in identifying characteristics of high-resolution (image) data [10]. Histology-based deep CNNs have demonstrated success in automating cancer grading; studies have shown that deep CNNs can perform on par with pathologists in prostate [11], [12], [13], breast [14], colon cancer [15], and lymphoma [16] grading.

Explainability techniques, which let pathologists verify DL-generated predictions, can help histology-based classification models function better as shown in Fig. 3. For instance, Hägele et al. used whole images of lung cancer slides [17] to apply the Layer Relevance Propagation (LRP) [18] approach in DL models that distinguish healthy and malignant regions. A relevance score was assigned to each pixel by the LRP algorithm, then amassed at the cellular level, and compared with pathologists' findings. These scores were subjected to evaluat impact of various data biases on the performance of DL model at cellular level [17]. Such findings are helpful for software developers and clinicians to explore new aspects of the DL model in the development and operation phases. Semantic segmentation is not only helpful in explainability and classification but also in the localization of specific areas of histopathology images. Generative adversarial network (GANs) is an essential method for the execution of semantic segmentation [19]. GAN, a generative neural network-based DL approach, is comprised of a generator (label each pixel of an image) and discriminator (classify the predicted labels) components [20]. A generator based on the CNN approach was used by Poojitah and Sharma for the classification and prediction of prostate cancer [19]. It was observed that the GAN annotations help the CNN classifier in tissue mapping which is in parallel with the findings of a pathologist, which enlightens the significance of the DL model in prediction and decision-making.

Transcriptome analysis-based molecular subtyping of cancer is helpful in diagnosis, treatment and prognosis. Such molecular subtyping has been performed for malignancies of the breast [21] ovaries [22], colorectal [23], and skin [24]. The cancer subtyping is performed by computational approaches viz; k-nearest neighbours and support vector machines (SVMs) but these are prone to biases because of their reliability on signature genes and omission of eminent biological information [25], [26]. These limitations can be overcome by the DL approach as it assimilates algorithmic patterns from the transcriptome. In comparison with general ML approaches (logistic regression, gradient boosting machine, SVM, and random forest), a DeepCC-trained neural network depicts high, sensitivity, specificity, and accuracy when tested for gene expression through microarray by using TCGA-RNAseq data of breast and colon cancer [27]. Furthermore, neural network-based molecular subtyping of ovarian and gastric cancers [28], and lung cancer [29] has been performed successfully by using transcriptome data. It can be concluded that the DL method is a reliable approach for molecular subtyping of cancer by using transcriptome-generated large data sets and is flexible to include earlier reported information to augment its performance [30].

The prediction of subtypes can be enhanced by multimodal approaches that integrate transcriptomic data with data from other omics. For better prediction of breast cancer subtype PAM50, two CNN approaches were trained independently on gene expression and copy number alterations (CNAs) in a novel multimodal approach [31]. This approach outperformed CNNs trained on individual data types. Multimodal learning techniques are anticipated to proliferate in cancer diagnosis as multi-omics analysis gains popularity. The clinical use of these strategies, however, might be hampered by the difficulties in producing multi-omics data of patients in the clinic as countered to those bio-banked for studies. Digital histopathology images can serve as a substitute for transcriptomic-based techniques for genetic subtyping and are an essential component of the cancer process [32].

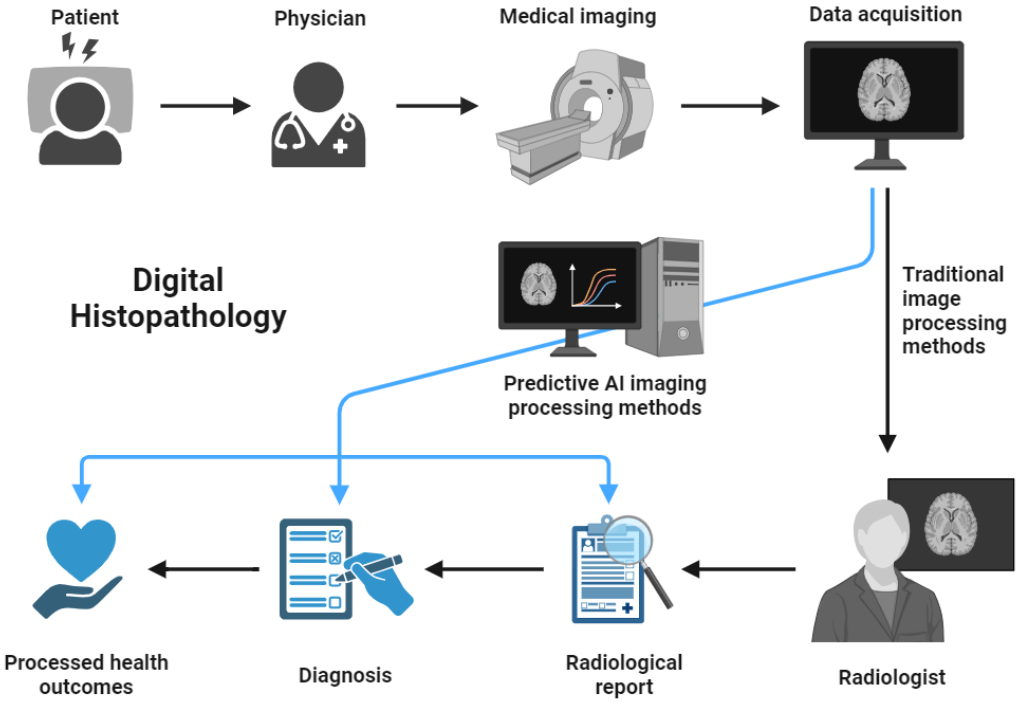

Fig. 1. Digital Histopathology revealed more features and enhanced examination skills of health professionals for early detection and control of cancer

3.2. Diagnosing Cancers of Unknown Origin

As the tumour origin occasionally determines treatment methods, identifying the main cancer site might be crucial in the diagnostic procedure as it can serve as a major predictor of cancer's clinical behaviour [33]. On the other hand, cancers of uncertain primary (CUPs)—metastases with an unclear origin—make up 3–5% of all cancer cases [34], [35]. Metastatic cancers show distinct patterns in their transcriptome, methylation, and genomic profiles

that can identify the original tissues [36], [37], [38]. When applied to these omics data, traditional machine learning techniques like regression and SVMs can predict the genesis of tumours; however, their predictive power is often limited to a small group of genes, making it difficult to predict a wide variety of cancer types and subtypes. On the other hand, DL algorithms have access to a vast array of transcriptome and genomic characteristics. Predicting the genesis of cancer has also proven to be a useful application of deep learning techniques that utilize transcriptome data [39], [40], [41]. Based on the popular CNN model Inception, the CUP-AI-Dx algorithm produced comparable outcomes on 32 cancer types from ICGC and TCGA [40]. These models classify cancer based on their transcriptomic data into clinically important subgroups which depict the potential of DL model for the future. Besides the use of genomic and transcriptomic data sets, the development of another model named TOAD proficient in whole slide images (WSIs) was capable of predicting the status of metastasis in the body simultaneously and also gave the origin of 18 types of tumours [42]. In addition, this model also assigned an explainability technique called attention [43] to allocate diagnostic scores relevant to image sections and showed that those image regions exposed to cancer cells participated maximum to both metastasis and cancer source decision making. These findings suggested that the TOAD model can focus on biologically and clinically appropriate image arrangements and become a good contender for clinical placement.

3.3. Cancer Prognosis and Survivability

Prognosis prediction of cancer is an important tool in clinical oncology, as early diagnosis of expected pathways of disease and chances of persistence can help in making decisions related to cancer diagnosis. Application of deep learning models in genomics, transcriptomics, proteomics, and other types of data can predict cancer prognosis and survival of the patient [44], [45], [46], [47]. One of the most widely used methods in the prediction of survival is the Cox proportional hazard regression model (Cox-PH) [48], [49], [50], and this is a linear regression-based multivariate model giving correlations between the predictor variable and survival time of the patient. The main challenge faced by scientists in applying Cox model is its linear nature, as this can potentially abandon the complex datasets and other non-linear regression variables [51]. In contrast, deep neural networks could surpass this task as they are non-linear.

Surprisingly, many research studies have integrated the Cox model into DL and instructed the models of transcriptomics for precise prediction of prognosis [46], [47]. From these approaches, Cox-net was a ground-breaking method that revolutionized the diagnostic and prognostic approach and made the Cox linear regression model the yield stratum of neural networks, by using billions of deep features mined by unseen layers as an input for the Cox model [52]. The Cox-net model was expert in RNA-sequence data from ten TCGA cancer types and benchmarked alongside two variants of Cox-PH (Cox-Boost and Xox-PH). Cox-net displayed superior accuracy and became the only model that uniquely identified the main pathways comprising p53 signaling, junctions to adhere, and endocytosis, showing that the amalgamation of neural networks and the Cox-PH model has the potential to apprehend biological information related to prognosis prediction. Huang et al. confirmed the potential of deep learning [46] and found that 3 different types of deep learning models of Cox regression (Cox-nnet, AECOX [46], and DeepSurv [52] outperformed Cox-PH and traditional models of ML. DL methods with biological information elucidated the key factors for the survival of various features.

For this aspect, the most advanced DL approaches are PASNet [53] and Cox-PASNet (cox regression) [54]. A pathway layer is inserted between the hidden layer and input layer of the neural network and a pathway will be represented by every node of the pathway layer based on the database viz; KEGG [55] and Rectome [56]. Where the relationship of the gene pathway will be depicted by the connection joining two layers. The weight of these pathway nodes varies among survival groups. PASNet and Cox-PASnet analyze the weight and connection of genes with each node for determination of actionable genetic characteristics of clinical cases viz; ovarian cancer and glioblastoma multiforme (GBM) [53], [54]. Cox-PASnet successfully recognized the PI_3K pathway (associated with invasion, proliferation, and migration of tumours) and $MAPK_9$ gene (the most influential gene involved in carcinogenesis) in GBM [57], [58]. For the incorporation of molecular pathways in the prognosis of cancer, GCNN-explainability is the latest model [59] and it relies on gene expressions regulated by a PPI from protein database for metastasis prediction.

The LRP, an explainability method, has been used to recognize and analyze the biological relevance of genes associated with cancer prediction [18], [59]. Further analysis depicts the role of various genes (i.e. EGFR and ESR1) in oncogenesis, molecular subtyping, and therapeutic measures [59]. In addition to transcriptome data-based prediction, CNN models infer survivability from histopathology images of cancer cases viz; kidney [60], brain [61], hepatic cells [62], colorectal [63], and mesothelioma [64]. MesoNet integrated explainability algorithm (CHOWDER) with stained tissue samples of mesothalmia to elaborate the role of stroma cells (involved in inflammation and vacuolization) in predictions of survivability [64] without the assistance of a pathologist. It can be concluded that MesoNet is an effective approach to assist clinicians in the identification of known and unknown histological features and their role in survivability. The multimodal DL approach along with incorporating histopathological pictures and omics data improves personalized therapy and patient's prognostic assessment.

Most of the multimodal prognostic research has focused on three sections including cross-modal assessment of prognostic attributes, individual characteristic extraction from a single mode, and multimodal data amalgamation. The PAGE-Net model used a CNN to generate COX-PASNet and WSI representations for the extraction of information about genetic pathways [65]. PathME approach is an excellent choice of clinicians for identification of actionable biomarkers within large omics data sets and it is not specific to any malignancy. Principle component analysis (PCA) [66], [67] used to evaluate gene expression, methylation and mutation in eigengene vectors [68]. These vectors were then coupled with histopathological characteristics derived by CNN to predict survival. Although these techniques have the potential to combine multi-omics data with histopathology data, they are less clinically acceptable and less explicable than PAGE-Net [65] or PathME [69], as the conversion of genes into eigengenes, complicates the investigation of cross-modality interactions.

3.4. Precision Oncology

Precision medicine holds the potential to enhance patient survival by optimizing patient management and therapy using high-resolution omics data. Understanding the tumour microenvironment (TME) and cancer genetics is a crucial component of precision oncology. With the use of DL, it is possible to decipher the intricate heterogeneity of TME and deduce significant genomic traits from easily accessible histopathological data, hence facilitating precision oncology. It has been demonstrated that genomic features such as microsatellite instability (MSI) and tumour mutation burden (TMB) are significant indicators of immunotherapy response in a variety of cancer types [70], [71], [72], [73]. Sequencing is currently costly and not always accessible in clinics, is necessary for assessing these features.

Regularly used histopathological pictures have the potential to provide a window into genomic features and could eventually help predict molecular features that are clinically significant without requiring tumour sequencing Fig. 4. The CNN techniques attempted to calculate TMB for every area in an image [74], [75], which would make it possible to study the histological characteristics connected to molecular heterogeneity. Investigations represent proof-of-concept, nevertheless, and the models that were created might eventually be modified to forecast clinically significant molecular characteristics that aren't often evaluated. Future research on histopathology-based genetic inference is therefore necessary, with the realization that for these DL models to completely replace the tests used today, their accuracy must be extraordinary.

TME is important for the development, metastasis, and response to treatment of cancer [76], [77]. Nonetheless, a great deal is still unclear about the intricate chemical and cellular interactions that occur within the TME. Large publicly accessible databases of genomic, transcriptomic, and histopathological data, along with the growing application of deep learning in cancer research, have established a robust technical foundation for the application of neural networks in characterizing TME heterogeneity. Immune cell types that infiltrate, such as CD^{4+} and CD^{8+} T cells, have the potential to be significant indicators of the response to immunotherapy [78], [79]. Transcriptomic data (or methylation data) can be used by traditional machine learning techniques to precisely estimate the compositions of TME cells [80], [81].

Unfortunately, most of these techniques rely on either selecting a small number of CpG sites that are biased toward previously identified biomarkers or creating characteristic Gene Expression Profiles (GEPs). This may result in models that are biased and prone to noise, making it difficult to find new genetic biomarkers. To find the best features without using GEPs, DL techniques can be trained on the entire transcriptome or dataset. MethylNet (recently developed DL TME technique) additionally integrated the SHAP explainability technique to measure the significance of every CpG site for deconvolution [82], [83].

Future deep-learning techniques are anticipated to investigate the merging of histology and omics in the context of tumour immune landscape profiling [84]. Furthermore, single-cell transcriptomics (scRNA-Seq) data should be incorporated into future DL approaches to enhance TME predictions and perhaps understand transcriptomic description of distinct cell types. Nevertheless, to be therapeutically useful, these investigations still need to be validated and refined [85], [86].

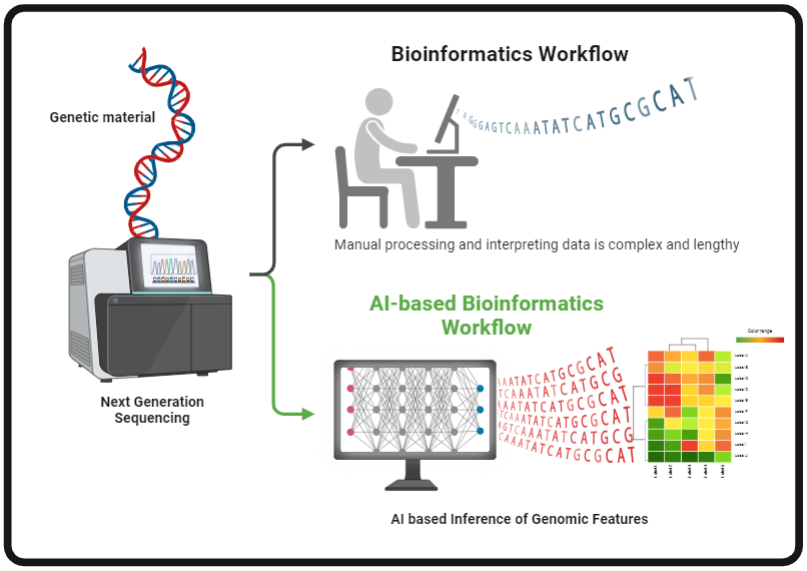

Fig. 2. The AI assisted genomic analysis revealed genomic features in a better way than traditional ones. Such depiction augments the early detection of cancer tissue and helps in the prevention of such conditions in features.

3.5. The New Frontiers

Spatial transcriptomics is an effective approach for TME evaluation by capturing high-resolution spatial heterogeneity of gene expression because it involves gene expression of a specific cell (as shown in Fig. 5) or region without disturbing their positional representation [87]. DL is an effective model for the analysis and interpretation of complex data sets. DL can forecast localized gene expression of a tissue sample by its assimilation with spatial transcriptomics and histopathological pictures. ST-Net, a DL approach, predicted the expression of tumour-associated genes in breast tumor by utilizing tissue spots from stained slides [87], [88]. The application of spatial transcriptomics (for prognosis prediction, classification of subtypes, and tumour heterogeneity understanding) will arise in the future with the decline in cost [89]. Furthermore, the gut microbiome (metagenome), an emerging field, plays a significant role in tumour therapy and its consequences [90], [91]. It was speculated that the integration of multi-omics datasets (genomics, microbiomics, transcriptomics, and proteomics) can map the omics profile of each patient which will help to explore new areas of research. Pharmacogenomics, genomic analysis-based prediction of drug response and mechanism of action as shown in Fig. 6, plays a pivotal role in precision oncology along with potential DL approaches [92]. The availability of individual omics datasets augmented the applications of DL and pharmacogenomics in oncology [93], [94]. Drug response and resistance viz; CDRscan [95], Dr.VAE [96], drug synergism viz; DeepSynergy [97], drug repositioning viz; deep-DR [98], and drug target interactions viz; DeepDTI [99].

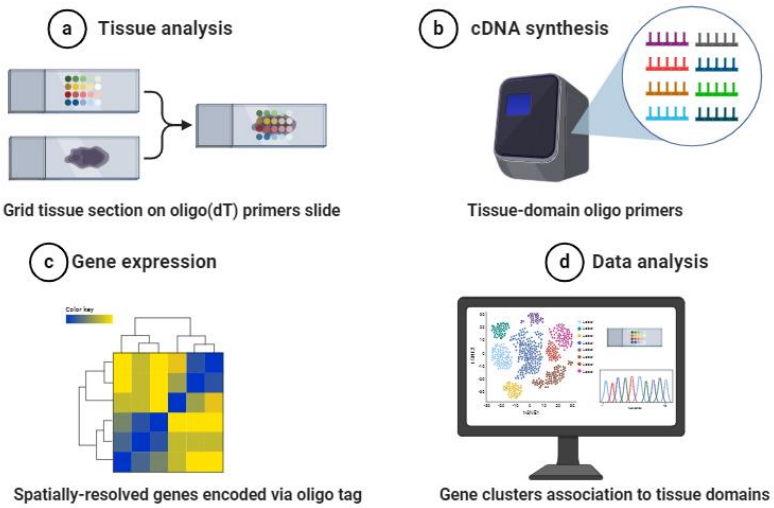

Fig. 5. Spatial transcriptomics is an effective approach for TME evaluation by capturing high-resolution spatial heterogeneity of gene expression (c&d) because it involves gene expression of a specific cell (a&b).

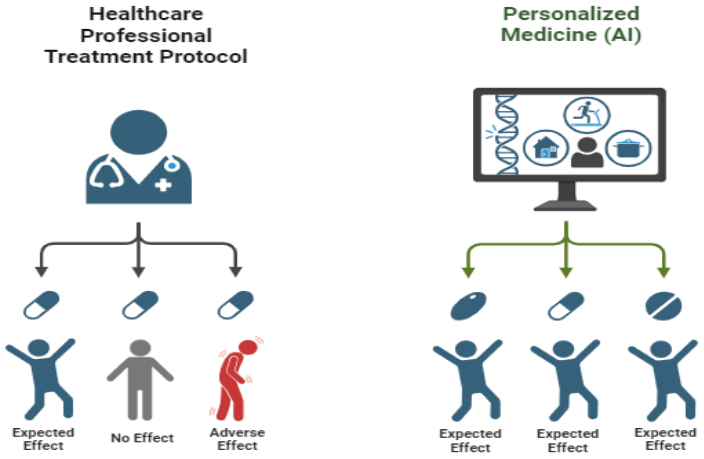

Fig. 6. Pharmacogenomics involves genomic analysis-based prediction of drug response and mechanism of action. AI based therapy generates expected outcome of the specific medicine and helps in early recovery of patients with no side effects.

4. CHALLENGES AND LIMITATIONS: ROAD TO CLINICAL IMPLEMENTATION

We provided an overview of potential applications of DL in the field of oncology but there are numerous challenges in DL implementation on a large scale in clinical settings. Here, we address the drawbacks and restrictions of DL in oncology and offer our recommendations for future developments. One of the main obstacles to applying DL to cancer is data unpredictability. For instance, staining intensities or characteristics could vary from lab to lab in immunohistochemistry. How DL systems would handle this intra- and interlaboratory variability is still unknown. Determining the precise processing used to create a library of sequences and the processed dataset is one of the main challenges with transcriptomic data. Any investigation should identify the basis and version of the gene model utilized since even qualities as fundamental as "the list of human genes" are subject to dispute and are regularly updated by multiple sources. Lists of genes and observed splice forms are published and updated. These processing paths should, in theory, yield the similar results, but there is no prescribed process to guarantee that this statement is true.

Developing and training DL techniques with strong generalization execution requires extensive, phenotypically defined datasets, which presents a hurdle for integrating DL into clinical practice. Omics-profiled cancer datasets of high quality are hard to understand under clinical conditions because of sample availability, cost, and quality issues. Furthermore, oncological samples of clinics are very few and kept as FFPE blocks, which leads to RNA degradation and crosslinking that makes them unsuitable for thorough molecular profiling. To get around this, explainability techniques like SHAP might be used on the existing deep learning models created in research settings to pinpoint the most important characteristics and create tailored summarizing workflows appropriate for samples of the clinical database.

The multi-modal DL models can use characteristics from one modality to supplement missing data from another, they should be investigated in conjunction with explainability. By pre-training deep learning models from other domains, transfer learning can also get around the problem of needing big datasets.

We anticipate seeing more DL models built for both the general prognosis and treatment response predictions as more clinical data are generated routinely and aggregated centrally in digital databases of health sectors [100]. More intriguingly, pathologists can save a substantial amount of time when training histopathology data annotation thanks to DL's capacity for "active learning," or the ability to learn from and improve accuracy with fresh training samples. Histopathology integrated DL model requires the annotation of a few training images by a pathologist and there is no further manual annotation with satisfactory performance of the model [101], [102].

4.1. AI Explainability and Uncertainity

For implementation and acceptance of DL models in clinical settings require designing to augment clinical outcomes. Human experts must be familiar with explanations and predictions related to uncertainties. Research has been increased on the role of AI in the health care system in recent years. Comprehensive biological studies are imperative for regulatory approval of DL as a diagnostic approach. The validation and cross-validation of DL-identified histopathological images are entailed with pathology review and genomic features respectively [17].

The validation of genetic features identified by DL against their identification by bioinformatic methods is entailed in genomics. There should be an output "I don't know" in the DL model to respond when predictions are questionable. Most deep learning applications discussed in this paper use point-estimate techniques, meaning that the predictions are just the best guesses with the maximum likelihood. In situations where accuracy is crucial, overconfidence in forecasts can lead to incorrect diagnosis or management decisions. An example of this would be identifying the primary location of cancer with only 40% certainty. Diagnostic tools should also be adept to refrain from generating predictions and seek the advice of medical experts when uncertainty estimations are too high [103]. These problems can be effectively addressed by probabilistic DL techniques that can quantify prediction uncertainty, including Bayesian DL [104], which have just begun to be used in cancer diagnosis tasks [105]. In the foreseeable future, we anticipate that probabilistic models will be widely used in oncology.

CONCLUSION

DL has the power to fundamentally alter cancer treatment and advance the field toward the goals of precision oncology. The progress, validation, and application of the decision support systems to enable precision oncology are expected to make use of artificial intelligence. We highlighted several exciting uses of DL in oncology in this review, including molecular subtyping, digital histopathology, histological inference of genomic features, tumor microenvironment, prognostication, and new fields like pharmacogenomics and spatial transcriptomics. Future applied deep learning in cancer is expected to center on the integration of omics data and medical imaging using multimodal learning to find biologically significant biomarkers as the field develops. It's exciting how multimodal learning and explainability together can produce fresh perspectives. More work is anticipated to be put into increasing the amount and caliber of medical data annotation when new technologies like multiplexed imaging, single-cell sequencing, and spatial transcriptomics become available. Finally, clinical validation of explainable DL approaches will be essential for DL to be adopted in ordinary patient care.

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Declarations

Author contribution. Writing original draft: M.U.; writing review and editing: F.S., A.A., M.U., and A.T.; conceptualization: A.S. and A.T.; formal analysis: MHAS.; investigation: F.S.; methodology: A.S., M.U., and A.A.; supervision: MHAS., A.T., and F.S.; visualization: M.U. After reading the published version of the manuscript, all authors have given their approval.

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Data and Software Availability Statements

Not Applicable

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