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Review

Transforming lung cancer care: Synergizing artificial intelligence and clinical expertise for precision diagnosis and treatment

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Abstract: Lung cancer is a predominant cause of global cancer-related mortality, highlighting the urgent need for enhanced diagnostic and therapeutic modalities. With the integration of artificial intelligence (AI) into clinical practice, a new horizon in lung cancer care has emerged, characterized by precision in both diagnosis and treatment. This review delves into AI's transformative role in this domain. We elucidate AI's significant contributions to imaging, pathology, and genomic diagnostics, underscoring its potential to revolutionize early detection and accurate categorization of the disease. Shifting the focus to treatment, we spotlight AI's synergistic role in tailoring patient-centric therapies, predicting therapeutic outcomes, and propelling drug research and development. By harnessing the combined prowess of AI and clinical expertise, there's potential for a seismic shift in the lung cancer care paradigm, promising more precise, individualized interventions, and ultimately, improved survival rates for patients.

Keywords: artificial intelligence; lung cancer; precision diagnosis; precision treatment; deep learning

1. Introduction

Nowadays, lung cancer remains at the forefront of global oncological challenges, contributing to a staggering 18.4% of all cancer-related deaths, inflicting profound societal distress and substantial economic consequences [1]. While cigarette smoking is implicated in nearly 85% of these cases [2], other factors such as environmental pollutants, occupational hazards, and genetic susceptibilities further accentuate the lung cancer landscape, especially among non-smokers. The increasing incidence of lung cancer underscores the pressing need for advancements in early detection methods and more effective therapeutic strategies. A pivotal factor determining the prognosis of lung cancer patients is the stage at which the diagnosis is made. Regrettably, existing diagnostic protocols often fall short, with symptoms predominantly surfacing during advanced stages, where metastasis has already occurred, culminating in a bleak 5-year survival rate of a mere 4% [3, 4]. However, traditional

diagnostic and treatment approaches face significant challenges in effectively addressing the complexities and individual variances associated with lung cancer.

Transitioning to diagnostic modalities, CT imaging, despite its ubiquity in lung cancer diagnosis, grapples with issues stemming from the intricate interpretation of voluminous data sets. Although pathological examinations furnish insights into tumor attributes via tissue biopsies [5], their inherent subjectivity coupled with inter-observer disparities erode their dependability. The domain of molecular diagnostics, with its focus on biomarker identification through meticulous genetic and molecular assessments [6] remains ensnared in the intricacies of data interpretation, necessitating specialized acumen and substantial resources [7]. On the therapeutic front, while a suite of treatments including surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy are routinely invoked [8], the heterogeneous nature of lung cancer introduces a myriad of challenges in curating a holistic treatment regimen. Factors such as tumor subtypes, genetic aberrations, and patient-specific attributes must be seamlessly integrated into the decision-making process. Interestingly, current evidence remains inconclusive regarding the augmentation of survival rates via induction, consolidation chemotherapy, or radiation dose escalation [9–11]. The nuances of inter-patient variability in both therapeutic responses and potential toxicities further convolute the treatment landscape. Therefore, the conventional armamentarium for lung cancer diagnosis and treatment is fraught with challenges, from data interpretation bottlenecks and demanding clinical workloads to the intricate art of clinical decision-making.

Recently, the rapid advancements in computer technology and statistical analysis have set the stage for the transformative role of Artificial Intelligence (AI) in the realm of lung cancer diagnosis [12–16]. Deep learning algorithms have emerged as a groundbreaking approach, revolutionizing the accuracy and efficiency of lung cancer detection and staging through the precise analysis of CT images [17–19]. Integration of AI with pathological images has enabled unprecedented advancements in tumor grading and staging, unlocking invaluable insights for treatment planning and prognostic assessment [20]. By harnessing the power of genomic analysis and biomarker identification [21, 22], AI paves the way for the realization of precision medicine, tailoring treatment strategies to the unique characteristics of individual patients [23, 24]. Moreover, AI acts as an indispensable partner in clinical decision-making, empowering clinicians to navigate complex treatment landscapes by offering reliable predictions of treatment response, potential side effects, and prognosis across diverse therapeutic modalities, including medical treatment, surgery, and radiotherapy [25–28]. Furthermore, a meticulous survey of recent literature from the last decade, conducted on the Web of Science's core collection with targeted keyword searches, yielded 918 pertinent articles. This wealth of research, represented in a comprehensive chord diagram (Figure 1), underscores the global endeavors to merge AI's prowess with clinical expertise. Hence, the seamless integration of AI into future clinical workflows holds immense promise, propelling the field of lung cancer care to new frontiers of innovation and improved patient outcomes.

This article provides a comprehensive overview of the development and applications of AI in lung cancer diagnosis and treatment. We discuss recent advancements in AI research, specifically focusing on its role in image recognition, staging, and prognostic prediction for lung cancer. Furthermore, we will discuss the application of AI in precision medicine, leveraging genomic analysis and biomarker identification to enable personalized treatment approaches. By providing valuable insights and guiding future research directions, this review aims to contribute to the utilization of AI for improved lung

cancer diagnosis and treatment. We also discuss the current challenges, opportunities, and the potential integration of AI into clinical practice to achieve individualized care for lung cancer patients.

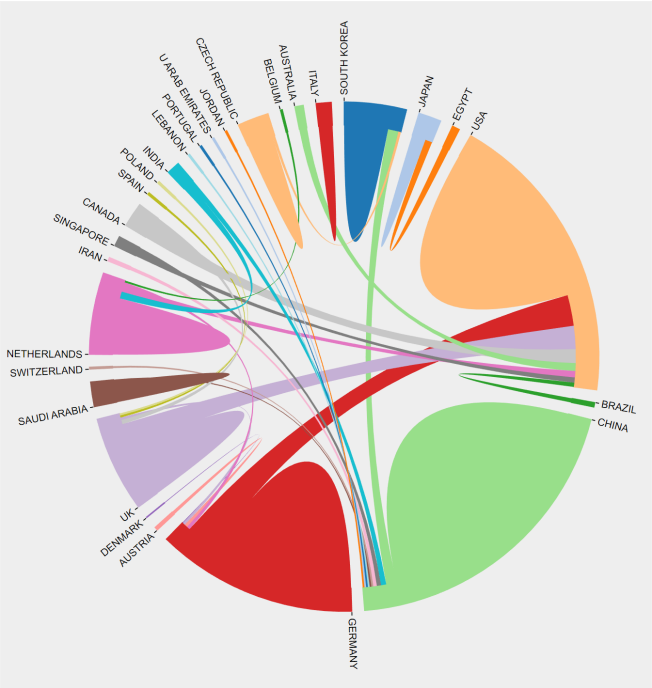

Figure 1. An overview of AI's revolution in lung cancer diagnostics.

2. Evolution of AI in lung cancer

Over the past decade, the field of lung cancer care has witnessed a remarkable transformation driven by the rapid evolution of artificial intelligence (AI) [29–31]. Figure 2 illustrates the significant milestones in the field of AI applied to lung cancer diagnosis throughout history.

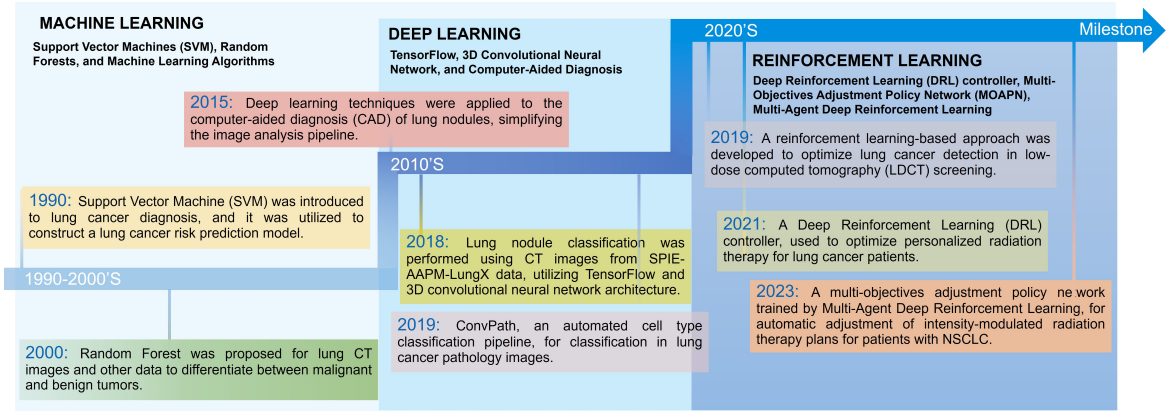

Figure 2. An overview of AI's revolution in lung cancer diagnostics.

In the early stages, machine learning algorithms were applied in lung cancer diagnosis. Traditional machine learning algorithms such as Support Vector Machines (SVM) and Random Forests were used

for processing and analyzing lung imaging data, enabling tasks such as tumor detection and classification [32, 33]. These algorithms relied on manual feature engineering, extracting and selecting predefined features for lung cancer diagnosis [34]. With the evolution of machine learning, researchers have used machine learning algorithms to identify unique radiomic features or genetic biomarkers associated with specific subtypes of lung cancer. For example, a study published in "Scientific Reports" in 2018 successfully differentiated between adenocarcinoma and squamous cell carcinoma using radiomic features extracted from CT images [35].

Deep learning refers to a machine learning method that has evolved from artificial neural networks. Around 2006, deep learning gained widespread attention with advancements in computing power and the availability of large-scale datasets [36]. Subsequently, AI has achieved significant breakthroughs in the field of lung cancer [37]. In 2015, deep learning techniques simplified the image analysis pipeline and achieved better discriminative results in the computer-aided diagnosis (CAD) of lung nodules, showing promise in improving prognosis for lung cancer [38]. In [39], lung nodule classification was performed using CT images from SPIE-AAPM-LungX data, utilizing TensorFlow and 3D convolutional neural network architecture, which had gained popularity for accurate classification of lung cancer. Notably, in [40], a deep convolutional neural network was trained on whole-slide images to accurately classify lung histopathology slides into adenocarcinoma (LUAD), squamous cell carcinoma (LUSC), or normal lung tissue, achieving performance comparable to pathologists. Moreover, commonly mutated genes in LUAD, suggesting that deep-learning models can aid in cancer subtype detection and gene mutation prediction.

Approaching the 2020s, AI in lung cancer diagnosis has started to integrate diverse types of data, such as genomics, clinical data, and pathology data [41–43]. By combining and jointly analyzing these different data sources, AI can provide a more comprehensive evaluation of lung cancer risk and prognosis, facilitating more accurate diagnosis and treatment decision support. For instance, Nair et al. [44] developed radiogenomics models from CT and FDG PET-CT images to predict EGFR mutations in non-small cell lung cancer (NSCLC), achieving promising accuracy in differentiating EGFR mutant from wild type tumors. The imaging signatures hold potential for pretreatment assessment and prognosis in precision therapy. Furthermore, to identify associations in non-small cell lung cancer (NSCLC), Singal et al. [45] demonstrated the feasibility of combining electronic health record (EHR)-derived clinical data with comprehensive genomic profiling (CGP), providing valuable insights into driver mutations' response to targeted therapy and tumor mutation burden's impact on immunotherapy response.

As reinforcement learning advances, AI applications in lung cancer are expanding to include autonomous decision-making and treatment planning [46]. In [47], a reinforcement learning-based approach was developed to optimize lung cancer detection in low-dose computed tomography (LDCT) screening, reducing the false positive rate while maintaining a high true positive rate compared to human experts. Considering patient-specific tumor features and daily fractionation, a Deep Reinforcement Learning (DRL) controller was developed to optimize personalized radiation therapy for lung cancer patients [48]. The DRL approach outperformed current clinical practice by adapting to different reward functions and exploring various treatment strategies.

Through significant advancements in imaging analysis, pathology interpretation, and molecular diagnostics, AI has emerged as a promising ally in revolutionizing lung cancer care.

3. The role of AI in lung cancer diagnosis

In this section, we explore the clinical applications of AI in lung cancer diagnosis, mainly including imaging and radiology, pathology, genomics, and molecular diagnostics [49]. Subsequently, in the ensuing section, we elucidate the extensive clinical applications of AI in lung cancer treatment, from personalized treatment [50]. This encompasses personalized treatment approaches, prognostication of treatment response, anticipation of prognosis, as well as advancements in drug discovery and development.

3.1. AI in imaging and radiology

The application of AI technology in the fields of imaging and radiology has opened up new possibilities for the early diagnosis and treatment of lung cancer [50]. Different imaging modalities, such as CT imaging, X-ray images, and MRI, are widely utilized in the clinical diagnosis of lung cancer [51]. By combining AI algorithms with medical imaging, it becomes possible to more accurately assess the nature, staging, and prognosis of tumors, providing patients with personalized and precise treatment plans. The integration of advances in imaging and radiology with AI technology holds great promise for the future development of lung cancer diagnosis and treatment [52]. Table 1 presents the AI applications in radiology and imaging for lung cancer diagnosis.

Table 1. AI applications in radiology and imaging for lung cancer diagnosis.

Year	Ref.	Modality	Methods	Results
2016	[55]	CT imaging	ConvNets-CAD	sensitivity (94.4%)
2018	[57]		A two-stage system based on 3D CNNs	sensitivity (91%)
2019	[56]		A novel automated pulmonary nodule detection framework with 2D CNN	sensitivity (86.42%)
2019	[59]		A deep learning algorithm	AUC (94.4%)
2019	[60]		DCNN	sensitivity (89.3%) specificity (83.3%)
2019	[61]		DCNN	accuracy (93.9%)
2018	[65]	X-ray	DenseNet-121	accuracy (74.43±6.01%) specificity (74.96±9.85%) sensitivity (74.68±15.33%)
2020	[67]		Modified AlexNet (MAN) with SVM and Softmax	accuracy (97.27%)
2020	[68]		Patch-based Multi-resolution Convolutional Networks	FAUC (98.2%) R-CPM (98.7%)
2018	[70]	MRI	K-means clustering CNN	accuracy (98.85%) sensitivity (98.32%) precision (99.40%) specificity (99.39%)
2019	[72]		CNN	accuracy (96.55%)
2023	[73]		RF CNN EBRNN	EBFNN accuracy (93%)

3.1.1. CT imaging

CT imaging plays a crucial role in the diagnosis of lung cancer. Through CT scans, doctors can obtain high-resolution images of the lung's structure, aiding in the detection of abnormal nodules, masses, or other lesions. Recently, the application of CT imaging in the diagnosis of lung cancer has been significantly advanced through the utilization of multi-view convolutional neural networks (ConvNets) and deep learning-based frameworks [53, 54].

A computer-aided detection (CAD) system was developed for pulmonary nodules by analyzing a set of nodule candidates from CT images and extracting 2D image patches from different orientations, utilizing multi-view convolutional neural networks (ConvNets). On 888 scans of the publicly available LIDC-IDRI dataset, this CAD system achieved high detection sensitivities of 85.4% and 90.1% at 1 and 4 false positives per scan, respectively [55]. Also for achieving accurate detection of pulmonary nodules in CT images, Xie et al. [56] proposed an automated framework for pulmonary nodule detection based on 2D convolutional neural networks (CNN). The offered framework achieved notable results with a sensitivity of 86.42% for nodule candidate detection on the LUNA16 dataset. Additionally, the framework achieved sensitivities of 73.4% and 74.4% at 1/8 and 1/4 false positives per scan, respectively, showing promising performance in false positive reduction. DeepMed, a two-stage computer-aided detection system for automatic detection of pulmonary nodules, achieved fast screening and generated candidate suspicious regions, utilizing a 3D fully convolutional network in the first stage. The second stage consisted of an ensemble of 3D CNNs, achieving a high sensitivity of 91% at a low false positive rate of 2 per scan on the LIDC dataset [57].

Accurate tumor detection is of vital necessity for Lung cancer's effective diagnosis and treatment [58]. Another research, based on the current and prior CT scans of patients, studied a deep learning-based lung cancer risk prediction model, which demonstrated remarkable accuracy in forecasting the likelihood of developing the disease. The model demonstrated exceptional performance, achieving a 94.4% area under the curve on the National Lung Cancer Screening Trial cases and yielding comparable results on an independent clinical validation set of 1,139 cases [59]. Recently, a deep convolutional neural network (DCNN) was developed to automate the classification of malignant lung cells in microscopic images. The DCNN achieved a classification sensitivity of 89.3% and specificity of 83.3%, comparable to a cytopathologist. Utilizing data augmentation techniques, a dataset of 60,000 image patches was generated to enhance the model's performance [60]. Figure 3A illustrates DCNN architecture for the classification of lung cytological images. In a different study, DCNN is also employed to automate the classification of pulmonary nodules in computed tomography (CT) images, as shown in Figure 3B. The advanced method achieved a significant improvement in classification accuracy, distinguishing between benign and malignant nodules with 66.7% accuracy for benign nodules and 93.9% accuracy for malignant nodules [61].

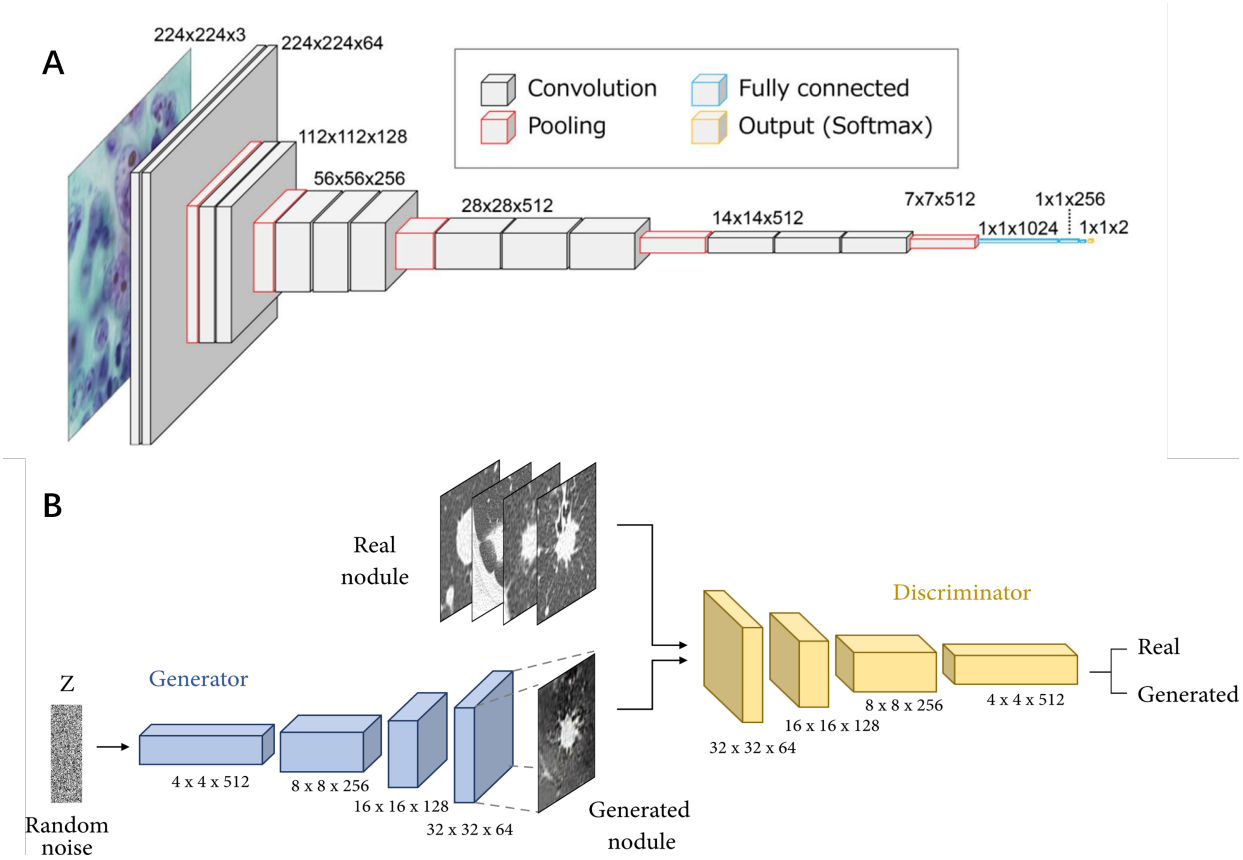

Figure 3. (A) DCNN architecture for classification of lung cytological images. We employed transfer learning on a pretrained VGG-16 model. The image specifies the types and dimensions of each layer in the network [60], (B) Architecture of the GAN used for nodule generation [61].

3.1.2. X-ray

Similarly, X-ray images play a fundamental role in the initial assessment of lung health. With AI applications, computer-aided diagnosis (CAD) systems can assist radiologists in pinpointing and characterizing lung lesions, leading to more precise and timely diagnosis [62–64]. Ausawalaithong et al. [65] utilized a 121-layer convolutional neural network (DenseNet-121) and transferred a learning approach to analyze and classify chest X-ray images for the diagnosis of lung cancer. This model achieved remarkable results with a mean accuracy of 74.43±6.01%, mean specificity of 74.96±9.85%, and mean sensitivity of 74.68±15.33%. CXR has relatively low sensitivity and specificity in the diagnosis of lung cancer, thus it is often necessary to combine other imaging examinations, such as CT scans, for further evaluation and confirmation of lung cancer [66]. Recently, both CT images and chest X-ray images were adopted to detect lung abnormalities and improve classification accuracy based on a DL framework. Researchers applied chest X-ray images (CXR) for initial deep learning (DL) classification and compared the performance with support vector machines (SVM). The DL model, based on a modified AlexNet (MAN) architecture, achieved an impressive classification accuracy of 92% in distinguishing between normal and pneumonia classes [67]. A study proposed a deep learning-based lung nodule detection method that utilized chest X-ray radiographs (CXR) to provide diagnostic support for early-stage lung cancer. They employed a patch-based multi-resolution convolutional neural network and utilized four different fusion methods for classification. It achieved a detection rate of over 99% for lung nodules when limiting the false positives per image (FPs/image) to 0.2 [68].

3.1.3. Magnetic resonance imaging (MRI)

In recent years, MRI technology has played a more and more crucial role in lung cancer diagnosis by providing high-resolution lung images, aiding in tumor detection and characterization [69]. Furthermore, the integration of artificial intelligence in MRI applications enhances diagnostic accuracy and efficiency through automated analysis and image recognition, leading to improved healthcare outcomes for patients. For example, to achieve the diagnosis of lung cancer using MRI images, Rustam et al. [70] proposed a novel approach combining Convolutional Neural Network (CNN) and Kernel K-Means clustering. The Anti-PD-1 Immunotherapy Lung dataset from The Cancer Imaging Archive was utilized, containing 150 healthy lung images and 250 lung cancer images. With 98.85% accuracy, 98.32% sensitivity, 99.40% precision, 99.39% specificity, and 98.86% F1-Score, these results shew immense efficiency and promise in MRI-based lung cancer diagnosis. MRI was broadly known as a valuable tool for lung cancer screening [71]. Also, an automated approach using MRI images was conducted to research and achieved high accuracy rates of 96.28% (conventional image processing) and 96.55% (CNN-based classification) for lung cancer detection. This finding suggested the potential of automated methods to assist in early diagnosis and improve patient outcomes [72]. In addition, Wahengbam et al. [73] employed image preprocessing and algebraic morphological operations to identify lung tumors, and utilized an Enhanced Backpropagation Feedforward Neural Network (EBFNN) for benign and malignant classification. Experimental results demonstrated that EBFNN outperformed other algorithms with an accuracy of 93%.

3.2. AI in pathology

AI has been widely applied in the field of pathology, encompassing tasks such as tumor classification and tumor microenvironment (TME) [74]. More researchers are devoted to it, aiming to explore the applications and advancements of AI in these areas to enhance diagnostic accuracy and prognostic assessment for lung cancer patients. Table 2 provides a comprehensive overview of the deep learning models for lung cancer pathology analysis.

Table 2. Summary of deep learning models for lung cancer pathology analysis.

Topic	Lung cancer subtype	Task	Model	Accuracy	Year	Ref.
Lung cancer classification	ADC	Maglinant vs. non-malignant classification	CNN	89.8%	2018	[77]
	Not specified		CNN	86.4%	2019	[78]
	ADC	Hisotological subtype classification	CNN	89.24%	2019	[80]
	NSCLC	PD-L1 status prediction	FCN	N/A	2019	[79]
	NSCLC	Transcriptomic subtype classification	CNN	N/A	2020	[81]
Micro-environment analysis	ADC and SCC	Necrosis positive vs. negative classification	CNN	N/A	2018	[83]
	ADC	Microvessel segmentation	FCN	N/A	2018	[84]
	ADC	Tumor vs. stromal cell vs. lymphcyte classification	CNN	90.1%	2019	[85]
	NSCLC	Tumor microenvironment segmentation	CNN	85.21%	2022	[86]

3.2.1. Tumor classification

Tumor classification involves categorizing tumors into different types and subtypes. In the diagnosis of lung cancer, different types of lung cancer may exhibit distinct biological characteristics and clinical behaviors, making accurate classification essential for tailored treatments. Artificial intelligence technology can aid pathologists in identifying and analyzing tissue sections, supporting the determination of tumor classification, enhancing classification accuracy and consistency, and providing more reliable evidence for personalized treatment decisions [75].

Actually, CNN was widely applied for accurate and automated classification of lung tumor histopathology images [76]. For example, a deep convolutional neural network (CNN) was employed to automatically identify tumor regions in lung cancer pathology images. The developed prognostic model based on tumor region shape effectively predicted a high-risk group with a 2.25 hazard ratio and 95% CI of 1.34–3.77, indicating worse survival compared to the low-risk group (p-value = 0.0022) after adjusting for age, gender, smoking status, and stage [77]. Figure 4A displays the flow chart of the analysis process. Vsaric et al. [78] introduced a fully automated method for detecting lung cancer in whole slide images of lung tissue samples. Employing convolutional neural networks (CNN) with two architectures (VGG and ResNet), the approach performed classification on the image patch level, offering a faster and more accurate alternative to traditional histopathological assessment. In another study, Sha et al. [79] utilized deep learning to predict tumor programmed death-ligand 1 (PD-L1) status from hematoxylin and eosin (H and E) whole-slide images of non-small cell lung cancer (NSCLC) samples, as shown in Figure 4B. The trained model accurately predicted PD-L1 status on the test cohort of H and E images (AUC = 0.80, P« 0.01), which suggested a correlation between PD-L1 expression and the morphological features of the tumor microenvironment. Similarly, a pipeline equipped with CNN was developed to assist pathologists in quantifying the percentages of distinct histological tumor growth patterns in lung adenocarcinomas (LAC). The model's accuracy was significantly better in the Cedars-Sinai Medical Center set (88.5%) compared to the MIMW (84.2%) and TCGA (84%) sets due to superior slide quality [80]. Figure 4C shows CNN trained with an augmented set of images from the training slides. Utilizing a quantitative histopathology analytic framework, major transcriptomic subtypes in both adenocarcinoma and squamous cell carcinoma ($P < 0.01$) can be successfully identified. Convolutional neural networks were built to classify histopathology images with high AUCs (>0.935) in identifying tumor regions and recapitulating expert pathologists' diagnosis (AUCs > 0.877) [81].

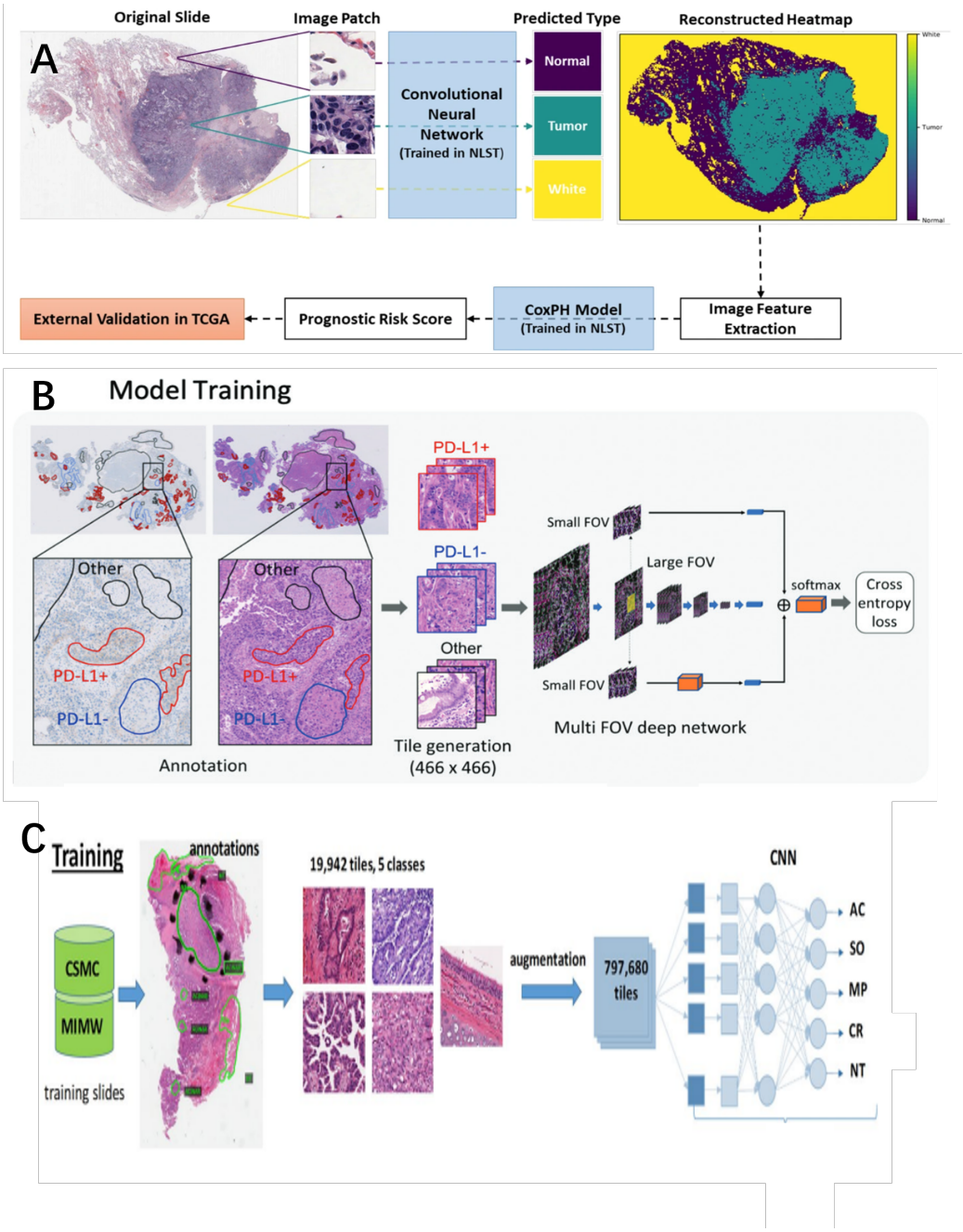

Figure 4. (A) Flow chart of analysis process. CNN, convolutional neural network; NLST, the National Lung Screening Trial; TCGA, The Cancer Genome Atlas [77], (B) Model training: matching areas on Immunohistochemistry and H and E slides were annotated [79], (C) CNN trained with an augmented set of images from the training slides [80].

3.2.2. Tumor microenvironment (TME)

The tumor microenvironment refers to the complex ecosystem of cells, blood vessels, immune cells, and various molecules surrounding the tumor [82]. It plays a crucial role in tumor growth, metastasis, and treatment responses. By leveraging artificial intelligence, efficient automated analysis of cell types and spatial distribution in tumor tissue sections can be achieved. This helps researchers gain deeper insights into the complexity of the tumor microenvironment, discover new treatment targets, and predict patient outcomes, ultimately providing valuable information for personalized lung cancer treatment.

Spatial infiltrate states in the TME could reflect particular tumor cell aberration states, as proved by a recent study. The study highlighted the underutilized potential of digitized H&E-stained images [83] of TCGA samples and presented TIL maps for 13 tumor types via a CNN. These maps revealed a correlation with overall survival and associations with specific T-cell subpopulations derived from molecular measures. In the same year, Yi et al. presented an automated microvessel detection algorithm [84] using fully CNNs in H&E stained pathology images. The identified microvessel features shew significant associations with patient clinical outcomes, providing insights into the tumor microenvironment (TME). ConvPath, an automated cell type classification pipeline [85], was presented for classification in lung cancer pathology images. The pipeline achieved an overall classification accuracy of 92.9% in the training dataset and 90.1% in the independent testing dataset. This approach offered valuable insights into the spatial organization of cells and their roles in tumor progression and the tumor microenvironment (TME). Figure 5A presents the feature extraction step of the ConvPath software. In the accurate classification of lung cancer tissue types, Rkaczkowski et al. [86] introduced a deep neural network, ARA-CNN, using 23,199 image patches from H&E-stained sections, which achieved per-class AUC ranging from 0.72 to 0.99. Figure 5B illustrates the annotated 26 of H&E tissue slides. The machine learning models utilizing the human-interpretable features attained a c-index of 0.723 for survival prediction and achieved an AUC of up to 73.5% for PDGFRB in the task of mutation classification, highlighting the potential of these features in predicting patient outcomes and cancer gene mutations related to the tumor microenvironment (TME).

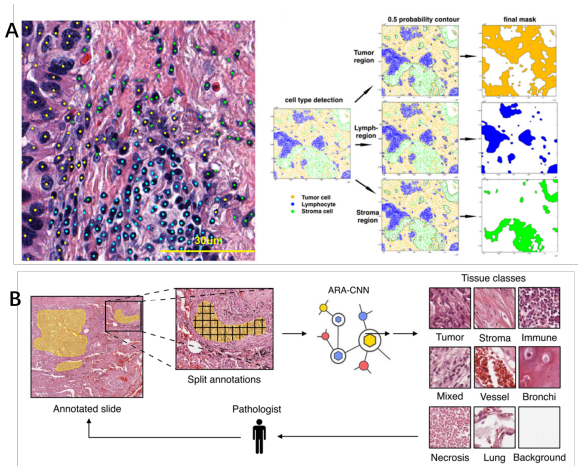

Figure 5. (A) Feature extraction step of the ConvPath software [85], (B) 26 of H&E tissue slides were annotated by an expert pathologist in an active learning loop with ARA-CNN, which resulted in the LubLung dataset and a trained tissue classification model [86].

3.3. AI in genomics and molecular diagnostics

In the study of lung cancer, gene and molecular diagnostics are important tools used by pathologists and clinical physicians to determine the patient's lung cancer type, and to devise personalized treatment plans [87, 88]. By analyzing the DNA, RNA, or protein levels of lung cancer patients, pathologists can identify the molecular characteristics of the disease, guiding treatment decisions and monitoring disease progression [89, 90].

3.3.1. Gene mutations and gene expression

In the field of lung cancer diagnosis, the integration of genetic mutation and gene expression data has become increasingly important for understanding the disease and developing effective treatment strategies [91, 92]. Researchers have leveraged advanced machine learning techniques to analyze these molecular features, enabling the identification of key genetic alterations and gene expression patterns associated with different subtypes of lung cancer [93].

In 2019, a study introduced a novel approach using spectral-convolutional neural networks (CNNs) to classify lung cancer by integrating protein interaction network data and gene expression profiles. The method outperformed traditional machine learning techniques like SVM and Random Forest in terms of accuracy, indicating its potential for enhancing gene expression-based lung cancer classification [94]. Recently, some researchers conducted various machine-learning algorithms to explore the gene expression profiles of lung adenocarcinoma (AC) and lung squamous cell cancer (SCC). By using powerful feature selection methods and incremental feature selection, they identified informative genes and constructed classification rules, shedding light on the transcriptomic differences between these two lung cancer subtypes [93]. Later, Wiesweg et al. [95] discussed the use of machine learning and context-sensitive feature selection on immune-related gene expression profiles in stage IV non-small cell lung cancer (NSCLC) patients. The researchers developed predictive models to identify patients with superior outcomes to PD-1/PD-L1 immunotherapy, independently of PD-L1 expression, based on a 770-gene panel. This AI-driven approach allowed precise prediction of response to immunotherapy in NSCLC by capturing the tumor immune context. In the same year, Khalifa et al. [96] proposed an optimized deep learning approach using binary particle swarm optimization with decision tree (BPSO-DT) and convolutional neural network (CNN) to classify different types of lung cancer based on tumor RNA sequence (RNA-Seq) gene expression data. The approach involved preprocessing the RNA-Seq data with BPSO-DT for feature selection and converting it into 2D images. Data augmentation was employed to overcome overfitting, and a deep CNN architecture was introduced for accurate classification of lung cancer types, achieving an overall testing accuracy of 96.90%.

3.3.2. Molecular biomarkers and biological markers

Molecular biomarkers and biological markers have been indicated crucial in lung cancer diagnosis, offering insights into the disease's mechanisms and guiding personalized treatments. Through advanced technologies and machine learning, distinct lung cancer subtypes can be identified, leading to more precise and effective therapeutic approaches, and revolutionizing lung cancer diagnosis and patient outcomes.

Early in 2019, the diagnostic potential of miRNAs in lung cancer was explored through a

support-vector-machine (SVM) model based on plasma miRNA biomarkers, clinical symptoms, and epidemiology data. The expressions of 10 plasma miRNAs were examined using SYBR Green-based quantitative real-time PCR, and significant differences were observed between lung cancer and control groups. The SVM model utilizing combined miRNA biomarkers showed promising accuracy (96.34%) and may serve as a novel, noninvasive method for auxiliary lung cancer diagnosis, involving the use of biomarkers and advanced machine learning techniques [97]. Then in 2020, Selvanambi et al. [98] presented a novel approach to enhance early prediction of lung cancer through the utilization of a higher-order recurrent neural network with the Levenberg-Marquardt model and glowworm swarm optimization algorithm to manage multimodal disease information. The proposed method demonstrated a significant improvement in accuracy (98%) compared to traditional optimized neural networks, emphasizing its relevance in the context of biomarker research for early diagnosis and prognosis of lung cancer. In 2022, Banaganapalli et al. [99] conducted a study to identify potential blood-based molecular biomarkers for chronic obstructive pulmonary disease (COPD) by analyzing dysregulated gene expression patterns in blood and lung tissues. Through computational analysis, 63 shared differentially expressed genes (DEGs) were identified between COPD and control samples. Twelve COPD hub gene-network clusters related to protein degradation, inflammatory cytokine production, airway remodeling, and immune cell activity were prioritized as potential blood-based genetic biomarkers for COPD diagnosis and prognosis.

3.3.3. Genomics and transcriptomics

By integrating artificial intelligence technology, genomics and transcriptomics enable the processing of vast amounts of biological data and employ machine learning algorithms to discover potential lung cancer-related features, accelerating the diagnostic process, enhancing accuracy, and providing more effective treatment options for patients [100].

Employing a Genomic Sequencing Classifier (GSC), Choi et al. [101] studied lung cancer diagnosis based on next-generation sequencing technology and artificial intelligence algorithms. The GSC effectively handles demographic shifts and interfering factors in gene expression, providing consistent performance across multiple cohorts. It identifies key genes and clinical covariates related to gene transcription, enabling accurate down- and up-classification of cancer risk in patients with inconclusive bronchoscopy results. Figure 6 illustrates the module eigengenes correlation with clinical factors. In 2021, a novel deep learning approach, Gene Transformer, used multi-head self-attention for efficient lung cancer subtype classification based on gene expression data. Unlike traditional algorithms, it identified relevant biomarkers without feature selection, resulting in improved performance and accurate classification of cancer subtypes [102]. Then Oka et al. [103] utilized long-read sequencing to comprehensively catalog aberrant splicing isoforms in non-small-cell lung cancers, identifying novel isoforms and potential neoantigens. A total of 2021 novel splicing isoforms were identified from 22 cell lines, some of which are validated by proteome analysis. The research revealed that disruptions of NMD factors UPF1 and splicing factor SF3B1 increased the proportion of aberrant transcripts, and certain isoforms had the potential to generate neoantigen candidates. Recently, to identify the transcriptome as a major source of phenotypic variation, Martine et el. [104] examined intratumor transcriptomic diversity in 354 non-small cell lung cancer tumors using paired whole-exome and RNA sequencing data. They linked metastasis-seeding potential to genomic and transcriptomic factors with machine learning, revealing the interplay between the

genome and transcriptome in intratumor heterogeneity and lung cancer progression. Moreover, allele-specific expression and ongoing APOBEC activity were discovered, emphasizing the role of gene transcription in lung cancer biology.

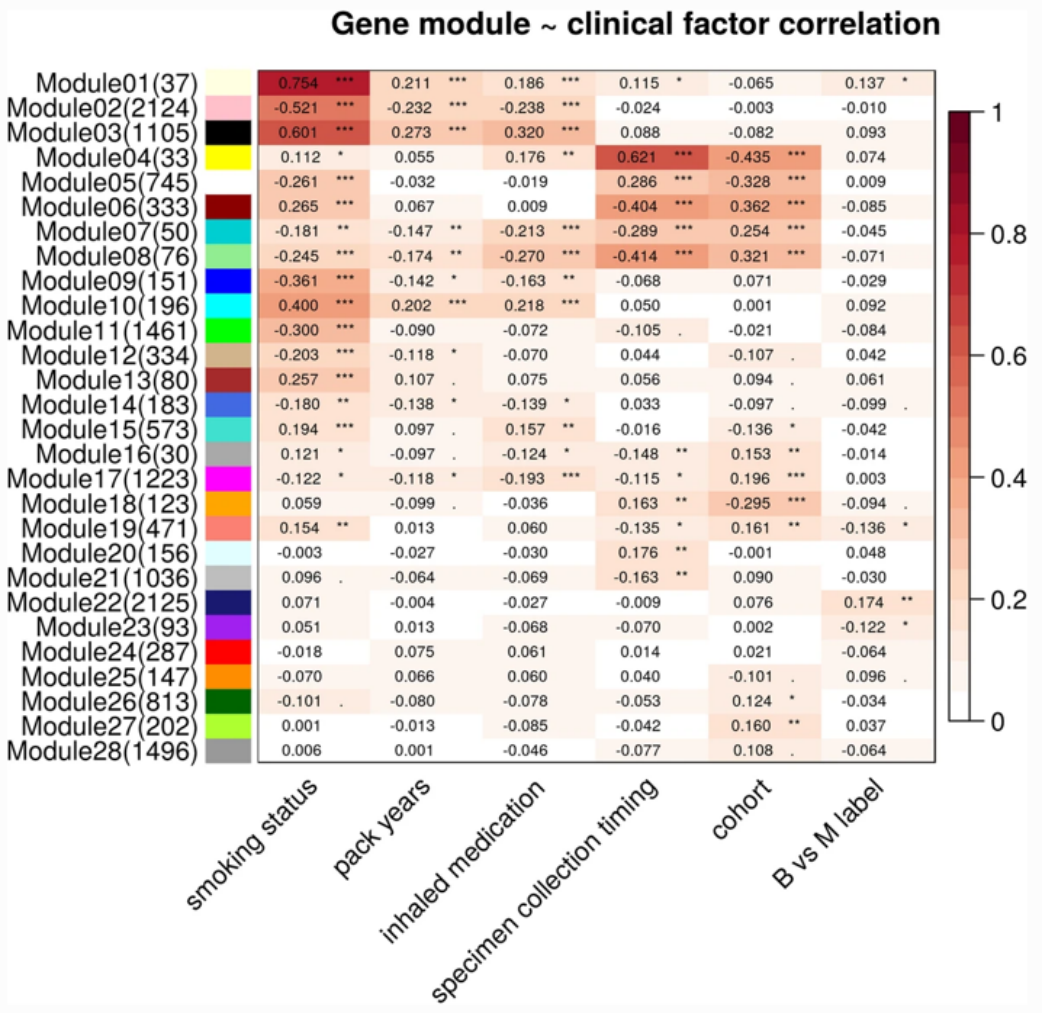

Figure 6. Gene correlation analysis (WGCNA): module eigengenes (listed by row) correlation with clinical factors (by column). Heatmap color is based on absolute Pearson correlation. Legend for p-value significance: '***' $0 < \text{p-value} \leq 0.001$; '**' $0.001 < \text{p-value} \leq 0.01$; '*' $0.01 < \text{p-value} \leq 0.05$; '.' $0.05 < \text{p-value} \leq 0.1$; ' ' $0.1 < \text{p-value} \leq 1$. Number of genes in each module is shown in parenthesis in row labels [101].

4. The role of AI in lung cancer treatment

4.1. AI in personalized treatment

Personalized treatment for lung cancer encompasses a range of modalities, including chemotherapy, targeted therapy, and immunotherapy. However, achieving optimal drug selection in this context is a complex task, considering the intricate interactions between the immune system, tumor cells, and the tumor microenvironment, as well as the classification and staging of lung cancer.

To address this challenge, AI-driven approaches have emerged as valuable tools in predicting drug sensitivity and optimizing treatment decisions for individual patients [105–107]. For instance, He et al. [108] presented a machine learning approach, named Kernelized Rank Learning (KRL), which partially addresses the prediction of drug sensitivity based on patient-specific effects per cell line. In non-small-cell lung cancer (NSCLC) patients, Luo et al. [109] introduced an efficient and cost-effective collaborative filtering method with ensemble learning, aiding in the selection of suitable compounds for personalized medicine. Moreover, researchers like Ciccolini et al. [110] have utilized dense longitudinal data to explore the mechanisms underlying the response or resistance to immunotherapy in lung cancer patients undergoing anti-PD1/PDL1 therapy, utilizing mathematical modeling and mechanistic learning algorithms. AI has also demonstrated promise in predicting EGFR mutation status in NSCLC patients through deep learning models based on 18F-FDG-PET/CT scans [111]. This non-invasive and precise method, known as EGFR-DLS, facilitates personalized treatment decisions, enabling the identification of NSCLC patients sensitive to EGFR-TKI or ICI treatments. Furthermore, AI has contributed to the development of patient-specific targeted drug screening frameworks, as proposed by Chang et al. [112], which analyze the effectiveness-to-cost ratio of target drugs to optimize treatment efficacy and cost-effectiveness for lung cancer patients. Additionally, Wang et al. [113] introduced a fully automated artificial intelligence system (FAIS) that leverages CT images to predict EGFR genotype and prognosis for lung cancer patients undergoing EGFR-TKI treatment. FAIS surpasses tumor-based deep learning models, providing a non-invasive approach to identify EGFR mutations and high-risk patients for TKI resistance. Machine learning classifiers were leveraged by Khorrami et al. [114] to extract radiomic texture features from baseline CT scans of non-small cell lung cancer (NSCLC) patients, predicting chemotherapy response and assessing their association with time to progression (TTP) and overall survival (OS). A pioneering approach by Song et al. [115] artfully harnessed multi-omics data and machine learning to identify predictive biomarkers for PD-1/PD-L1 inhibitors' efficacy in Chinese NSCLC patients, optimizing clinical responses among specific patient subgroups.

4.2. AI in predicting treatment response and prognosis

Predicting treatment response and prognosis is of paramount importance in lung cancer care, and AI has significantly advanced our ability to achieve more accurate prognostic capabilities and personalized treatment decisions for lung cancer patients.

In the realm of treatment response prediction, AI-driven approaches have demonstrated remarkable potential. Yu et al. [116] harnessed AI-driven analysis of histopathology images, RNA sequencing, and proteomics data to delve into the relationship between histopathology patterns and molecular abnormalities in lung adenocarcinoma. Their study successfully predicted histology grade and identified key pathways underlying tumor cell dedifferentiation. Similarly, a deep learning-based autoencoding approach was employed by Lee et al. [117], resulting in a robust survival prediction model showcasing significant differences in survival among patient subgroups in lung adenocarcinoma (LUAD) prognostication. In 2020, She et al. [118] applied a deep learning survival neural network, DeepSurv, to accurately predict lung cancer-specific survival in non-small cell lung cancer (NSCLC) patients, providing individualized prognostic information and treatment recommendations. Figure 7A shows the diagram of the study procedure. Furthermore, Wang et al. [113] proposed a fully automated AI system (FAIS) using CT images to predict EGFR genotype

and prognosis, presenting a valuable non-invasive auxiliary tool for personalized treatment decisions. Figure 7B displays the Workflow of the proposed FAIS and study design. Additionally, AI-driven quantitative image analysis and genomic biomarkers were utilized to predict cancer recurrence risk in early-stage lung cancer patients, leading to improved prognosis assessment for stage I NSCLC after surgery [119].

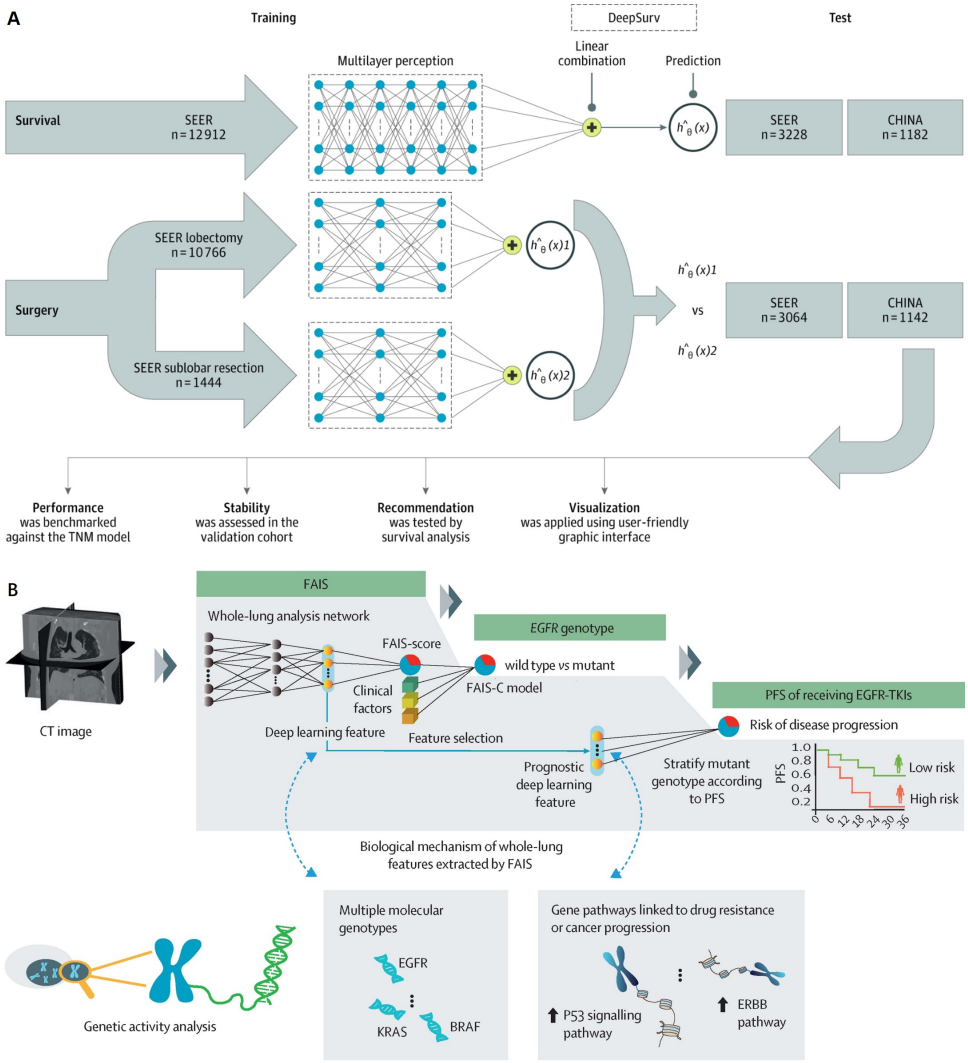

Figure 7. (A) Diagram of the Study Procedure [118], (B) Inference process of FAIS in predicting EGFR genotype and PFS in patients after receiving EGFR-TKIs. Mining associations between genetic activities and whole-lung features extracted by FAIS [113].

On the other hand, a distinct line of research has focused on prognostic survival prediction models for lung cancer patients. Computational and integrative analysis methods, including genome-wide relative significance (GWRS), genome-wide global significance (GWGS), and support vector machine (SVM) analyses, were employed by Liu [120] to enhance prognostic predictions for lung adenocarcinoma. Similarly, Malik [121] embarked on a multi-omics integration journey. The training

process of the model involved iterative feedback loops with weighted sampling to balance class distributions. After the initial model was developed, a rigorous validation process was undertaken using a separate cohort of LUAD patients not included in the initial training set. This meticulous methodology ensured the robustness and generalizability of the model. The resulting AI model, tailored to lung adenocarcinoma (LUAD) survival, showcased an impressive accuracy of 92.9% in classifying patients into distinct survival classes. Such advancements, which delve deep into the technical underpinnings of the AI models and their meticulous development processes, exemplify the potential of AI in paving the way for truly personalized treatments. Moreover, Wang et al. [122] introduced a prognostic survival prediction model using CT radiomics features and machine learning, achieving an accuracy of 88.7% and underscoring the potential of radiomics in predicting patient survival outcomes. Furthermore, a multi-stage framework was proposed by Johnson et al. [123], utilizing AI algorithms to predict the 5-year survivability of lung cancer patients, with Random Forests (RF) and Adaptive Boosting (AdaBoost) models outperforming others.

4.3. AI in drug discovery and development

The realm of drug discovery and development has been witnessing the growing application of diverse machine learning techniques, including naive Bayesian [124, 125], support vector machines [126], and advanced deep neural networks [127]. Leveraging the wealth of data from high-throughput screening, these methods achieve enhanced accuracy in predicting bioactivities related to targets and molecular properties. For instance, Zhavoronkov et al. [128] introduced GENTRL, a deep generative model based on AI, which rapidly identifies potent DDR1 kinase inhibitors, holding promise for expediting drug discovery. In the context of structure-based drug design, existing structural representations of target proteins, acquired through methods like X-ray diffraction, NMR, or molecular simulation, play a vital role in designing and optimizing potential drug candidates with precision and specificity [129–131]. Artificial intelligence (AI) algorithms, as demonstrated by Trebeschi et al. [132], excel in identifying radiographic biomarkers linked to immunotherapy response in melanoma and non-small-cell lung cancer (NSCLC) patients. These noninvasive biomarkers hold the potential to predict immunotherapy response and facilitate patient stratification for improved treatment outcomes. Additionally, Coundray et al. effectively employed inception-v3 with TCGA histopathological images to extract morphological features associated with gene mutation states, successfully predicting frequently mutated genes like EGFR, showcasing the potential of noninvasive and cost-effective gene mutation prediction using image data.

As drug discovery efforts progress, virtual screening emerges as a key aspect of computer-aided drug design, offering a cost-effective means to identify potential lead compounds. Researchers have harnessed the power of AI algorithms to analyze and predict drug-receptor interactions, a crucial step in identifying promising drug candidates. For instance, Wang et al. [133] utilized structure-based virtual screening and molecular dynamics simulations to identify T1551, a potential protein arginine methyltransferase 5 (PRMT5) inhibitor in non-small-cell lung cancer. Similarly, potential lung cancer inhibitors targeting the Rab39a protein were identified through a structure-based drug discovery approach, employing homology modeling and virtual screening techniques, as demonstrated by Haredi et al. [134]. Furthermore, the use of advanced computational methods and molecular docking allowed the design of a novel curcumin analogue, CUCM-36, as a selective inhibitor for EGFR mutations in non-small cell lung cancer (NSCLC), showcasing the potential of AI in discovering

promising anti-EGFR compounds for lung cancer treatment [135]. AI virtual screening, as utilized by Udhwani et al. [136], highlighted another promising candidate for lung cancer therapy, identifying potential inhibitors for PD-L1, a critical protein involved in lung cancer progression. Additionally, Patel et al. utilized virtual screening techniques, including computer simulations and molecular dynamics simulations, to identify potential novel allosteric inhibitors for overcoming drug resistance caused by EGFR T790M/C797S mutations in lung cancer patients [137].

5. Future perspectives: potential and challenges

Unlike other studies that tend to focus solely on the technical implementation or clinical benefits of machine learning in lung cancer care, this article embarks on a holistic exploration of AI's application across multiple disciplines within the domain, including imaging, radiology, pathology, and genomics. These studies demonstrate the broad potential of AI in lung cancer diagnosis, which is expected to have a positive impact on the future of lung cancer diagnosis and treatment. In the domain of radiology and imaging, AI stands to redefine how lung cancer detection and evaluation are performed. Deep learning frameworks, including convolutional neural networks, can now assimilate multi-modal imaging data, such as CT scans and MRIs, rendering a detailed, precise assessment of tumors. Specifically, AI augments the potential to delineate tumor boundaries, recognize early-stage lesions, and even predict tumor growth trajectories based on imaging data. This approach reduces interpretation time and expedites the identification of lung lesions, which results in timelier and more accurate diagnoses. AI's capabilities extend to pathology where it is poised to refine tumor classification and provide a deeper understanding of the tumor microenvironment (TME). The advancement of AI-powered algorithms not only improves the accuracy and efficiency of tumor classification, but also assists pathologists in devising more personalized treatment strategies. At the intersection of genomics and molecular diagnostics, AI shines as a key player in the fight against lung cancer . Through machine learning techniques, AI can now pinpoint novel genetic mutations or recognize specific gene expression patterns indicative of various lung cancer subtypes. AI aids in converging genomics and transcriptomics data, revealing intricate details about intratumor heterogeneity and potential tumor evolution pathways. In conclusion, as the field continues to evolve, AI is expected to drive significant advancements in early detection, accurate diagnosis, and personalized treatment of lung cancer, ultimately contributing to improved patient outcomes.

Indeed, addressing the potential obstacles and challenges in applying AI to lung cancer diagnosis is a crucial aspect of understanding the broader implications of this field. Concerns surrounding data privacy and security, technical interpretability, and clinical integration are particularly noteworthy [138, 139]. As we continue to leverage AI's potential in lung cancer diagnosis and treatment, the issue of data privacy and security rises to the forefront [140]. The use of patient data is essential to train AI algorithms, but this must be accomplished without compromising patient confidentiality and privacy. Ensuring robust anonymization measures, along with ethical guidelines, is essential to protect against unauthorized access or breaches. The interpretability, or lack thereof, of AI technology, presents another considerable challenge [141]. 'Black box' algorithms, where the decision-making process is not easily understandable by humans, can limit the clinical adoption of AI due to the difficulty in ascertaining how these algorithms arrive at their decisions. Increasing interpretability will build trust, improve collaboration between healthcare providers and AI systems,

and enhance patient outcomes. Integration of AI into clinical workflows also presents difficulties. Existing infrastructures may need significant modifications to accommodate AI. The need for AI solutions to work with various medical systems and technologies, as well as training medical professionals to work with AI, calls for attention [142]. Overcoming these challenges necessitates a balanced consideration of the ethical, technical, and practical implications of AI's transformative potential in healthcare. However, it is equally essential to discuss the ethical and regulatory considerations arising from these technical and practical challenges.

Ethical considerations and regulatory measures indeed play a significant role in the adoption and integration of AI in the healthcare sector, including its application in lung cancer diagnosis and treatment [143]. In terms of ethics, obtaining informed consent stands out as a priority [144]. As AI's role in patient care expands, it is essential to ensure transparency in data usage and obtain patients' consent. Furthermore, the potential biases in AI, originating from unrepresentative or skewed datasets, necessitate the use of diverse and representative data to guarantee fair healthcare outcomes. Regulatory challenges predominantly center around the standardization of AI applications [145]. Given the current lack of universal standards for AI in healthcare, there is an urgent need to establish stringent norms. These should guarantee the safety, reliability, and validity of AI tools, encompassing aspects like algorithm development, clinical validation, post-market surveillance, and a clear framework for accountability in the event of AI-related incidents. Lastly, legal frameworks may require adjustments to accommodate AI's expanding role, particularly concerning liability in case of treatment failure or misdiagnosis. Addressing these ethical considerations and institutional measures is a complex yet necessary task [146]. It requires a multidisciplinary approach, with active collaboration between AI specialists, healthcare professionals, ethicists, and policymakers. Only with the proper ethical and regulatory structures in place, can we ensure the safe and effective use of AI in lung cancer diagnosis and treatment.

6. Conclusion

In conclusion, this article has provided a comprehensive survey of AI's role in the advancement of lung cancer diagnosis and treatment. We have delved into its various applications, including its role in image recognition, staging, and prognostic prediction. We also explored the transformative potential of AI in precision medicine, enhancing individualized treatment through the use of genomic analysis and biomarker identification. Additionally, we have discussed the application of AI in diverse clinical scenarios, spanning from imaging and radiology to pathology and molecular diagnostics. AI's impact also extends to the prognosis of treatment response and advancements in drug discovery and development, marking its significant contribution to personalized lung cancer care. Yet, the journey of integrating AI into the lung cancer care paradigm is not without its challenges. Data security, algorithm transparency, and clinical integration issues stand out as significant hurdles. The future prospects include refining AI algorithms for even greater accuracy, developing standardized protocols for integrating AI into clinical practice, and ensuring that the technology remains patient-centered and ethically grounded. We have emphasized the vital role of AI in lung cancer treatment and its substantial potential to revolutionize patient care. As we navigate the complexities of this technological frontier, we remain hopeful about the potential for AI to significantly improve patient outcomes and pave the way towards truly personalized care.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there is no conflict of interest.

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