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REVIEW

Innovative technologies and their clinical prospects for early lung cancer screening

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Abstract

Background Lung cancer remains the leading cause of cancer-related mortality worldwide, due to lacking effective early-stage screening approaches. Imaging, such as low-dose CT, poses radiation risk, and biopsies can induce some complications. Additionally, traditional serum tumor markers lack diagnostic specificity. This highlights the urgent need for precise and non-invasive early detection techniques.

Purpose This systematic review aims to evaluate the limitations of conventional screening methods (imaging/biopsy/tumor markers), seek breakthroughs in liquid biopsy for early lung cancer detection, and assess the potential value of Artificial Intelligence (AI), thereby providing evidence-based insights for establishing an optimal screening framework.

Methods We systematically searched the PubMed database for the literature published up to May 2025. Key words include "Artificial Intelligence", "Early Lung cancer screening", "Imaging examination", "Innovative technologies", "Liquid biopsy", and "Puncture biopsy". Our inclusion criteria focused on studies about traditional and innovative screening methods, with an emphasis on original research concerning diagnostic performance or high-quality reviews. This approach helps identify critical studies in early lung cancer screening.

Conclusions Novel liquid biopsy techniques are non-invasive and have superior diagnostic efficacy. AI-assisted diagnostics further enhance accuracy. We propose three development directions: establishing risk-based liquid biopsy screening protocols, developing a stepwise "imaging-AI-liquid biopsy" diagnostic workflow, and creating standardized biomarker panel testing solutions. Integrating traditional methodologies, novel liquid biopsies, and AI to establish a comprehensive early lung cancer screening model is important. These innovative strategies aim to significantly increase early detection rates, substantially enhancing lung cancer control. This review provides both theoretical guidance for clinical practice and future research.

Keywords Artificial intelligence · Early lung cancer screening · Imaging examination · Innovative technologies · Liquid biopsy · Puncture biopsy

Abbreviations

AFB	Autofluorescence Bronchoscopy
AFP	Alpha-Fetoprotein
AI	Artificial Intelligence
CA-199	Carbohydrate Antigen-199
CAD	Computer-Aided Diagnosis
CAGE	Cancer-Associated Gene
CEA	Carcinoembryonic Antigen
cfDNA	Cell-Free DNA
CH_3	Methyl Group
circRNAs	Circular RNAs
CpG	Cytosine–Phosphate–Guanine
CTCs	Circulating Tumor Cells
CXR	Chest X-Ray Screening
CYFRA 21-1	Cytokeratin-19 Fragment Antigen 21-1
DNMT	DNA Methyltransferase
EMT	Epithelial–Mesenchymal Transition
FDG	Fluorodeoxyglucose
GAGE7	G Antigen 7

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GBU4-5	Globoside Binding Unit 4-5
MAGE A1	Melanoma Antigen A1
miRNAs	MicroRNAs
IARC	International Agency for Research on Cancer
LncRNAs	Long Non-Coding RNAs
LCCDE	Lung Cancer Cells-Derived Exosomes
LDCT	Low-Dose Computed Tomography
LUAD	Lung Adenocarcinoma
LUSC	Lung Squamous Cell Carcinoma
MRI	Magnetic Resonance Imaging
NBI	Narrow-Band Imaging
NGS	Next-Generation Sequencing
NLP	Natural Language Processing
NSCLC	Non-Small-Cell Lung Cancer
NSE	Neuron-Specific Enolase
p53	Tumor Suppressor Gene p53
PCR	Polymerase Chain Reaction
PET-CT	Positron Emission Tomography-Computed Tomography
PGP9.5	Protein Gene Product 9.5
SCC-A	Squamous Cell Carcinoma-Associated Antigen
SCLC	Small-Cell Lung Cancer
SOX2	Sex-Determining Region Y-Box2
TAAbs	Tumor-Associated Antigen Autoantibodies
TBNA	Transbronchial Needle Aspiration
WLB	White Light Bronchoscopy

Introduction

Lung cancer is one of the most prevalent and lethal malignant tumors worldwide and constitutes the primary cause of tumor-related mortality [1]. Pathologically, lung cancer can be categorized into Small-Cell Lung Cancer (SCLC) and Non-Small Cell-Lung Cancer (NSCLC). Approximately 85% of lung cancers are NSCLC, including Lung Adenocarcinoma (LUAD) and Lung Squamous Cell Carcinoma (LUSC), while the remaining 15% are identified as SCLC [1, 2]. According to the most recent data from the International Agency for Research on Cancer (IARC), new cases of lung cancer accounted for about 12.4% of the new cases of all malignant tumors, and the number of lung cancer-related cases accounted for about 18.7% of deaths from all malignant tumors [3]. Lung cancer exhibits the highest incidence rate in malignant tumors among the male population, while in the female population, its incidence rate is second only after that of breast cancer [4]. Research data show that the 5-year relative survival rate for lung cancer is merely 23%, in contrast with 90% for breast cancer and 98% for prostate cancer [4, 5]. The 5-year survival rate for patients with stage IV (advanced) lung cancer may be as low as 9%, whereas for those diagnosed with stage I (early) lung cancer, it can reach around 65%. Because of atypical symptoms and signs in the early stage, most lung cancer patients have already progressed into the advanced stage, accompanied by distant metastasis when they are diagnosed, which contributes to the high mortality rate and poor prognosis [6, 7]. Consequently, effective screening alongside prompt diagnosis and treatment for early-stage lung cancer patients constitutes a crucial strategy for enhancing survival rates and reducing the socio-economic burden.

Traditional screening methods primarily encompass three categories: imaging examinations, pathological biopsies, and conventional serum tumor biomarker tests. However, these conventional approaches face a technical dilemma of "high invasiveness yet low accuracy." While imaging examinations like Low-Dose Computed Tomography (LDCT) can improve early detection rates, they carry radiation exposure risks and exhibit high false-positive rates, potentially leading to over diagnosis and healthcare resource waste [8–10]. Although needle biopsies remain the diagnostic "gold standard" for pathological confirmation, their invasive nature may cause complications and preclude large-scale population screening [11, 12]. Serum tumor markers (such as CEA and NSE), while convenient for dynamic monitoring, (about 60%) and poor benign malignant differentiation capacity [13, 14]. These technical limitations have created a bottleneck in early lung cancer screening characterized by "high procedural risk yet suboptimal accuracy", urgently necessitating innovative diagnostic approaches that combine non-invasiveness with high precision.

In recent years, the emergence of liquid biopsy and AI technologies has brought revolutionary breakthrough to early lung cancer screening. Liquid biopsy achieves a technological leap of "minimally invasive sampling-precise detection" by analyzing Circulating Tumor Cells (CTCs), Cell-Free DNA (cfDNA), exosomes, and DNA methylation markers in biological samples such as blood and sputum [15]. Meanwhile, AI-assisted diagnosis significantly can improve the efficiency of LDCT image analysis and increase the accuracy of distinguishing benign from malignant nodules [16]. These technological advancements lay a scientific foundation for establishing a novel screening system characterized by "non-invasive but precise".

This review aims to evaluate the limitations of traditional screening methods, and explore the breakthrough advancements of liquid biopsy and AI technologies, and discuss their application value. It provides an evidence-based basis for optimizing the early lung cancer screening pathway, and helps achieve the prevention and control goals of "early detection, early intervention, and improved prognosis".

Imaging examination

Chest X-ray screening (CXR)

CXR is a crucial imaging examination method for pulmonary diseases due to its non-invasive, inexpensive, and easy to operate [17]. However, the CXR imaging quality is poor and susceptible to the structure of diseased tissues, leading to low sensitivity and a high misdiagnosis rate [18, 19]. Consequently, it is inadequate to screen for early lung cancer effectively [20]. In recent years, many studies have explored integrating CXR with other diagnostic techniques to enhance early lung cancer screening accuracy such as Sachithanandan et al. preliminarily demonstrated that integrating CXR with AI can increase early lung cancer screening accuracy [21]. Kwak et al. also found that the use of AI technology in CXR can improve diagnostic efficiency while yielding more clinically significant diagnostic findings [22]. Further research is necessary to determine whether the advantage of CXR can be widely used in the early screening of lung cancer.

Low-dose computed tomography (LDCT) imaging

LDCT, the most commonly used imaging method for early lung cancer screening, has a significantly higher sensitivity than CXR and can accurately localize normal and cancerous tissues in patients [5, 23]. The lung nodule diameter measurement using LDCT is unsuitable as an imaging biomarker for effective lung cancer risk stratification. However, volume doubling time can serve as a valuable imaging biomarker to help distinguish between benign and malignant tissue lesions [24]. LDCT exhibits a high detection rate for early-stage lung cancer and is regarded as a well-recognized method for the early screening of lung cancer, which can significantly reduce mortality rates [8, 25, 26]. Ideally, lung cancer screening should be performed annually, but this poses a significant burden for current radiological resources [27]. Therefore, LDCT is more appropriate to implement a lung cancer screening for high-risk populations. For example, the United States Preventive Services Task Force (USPSTF) updated national screening guidelines in 2021, recommending that asymptomatic individuals aged 50–55 years, who have a 20-pack-year smoking history, and current or former smokers who quit within 15 years, should conduct annual LDCT screening [8]. LDCT has been demonstrated to decrease lung cancer-related mortality by 20–24% in two pivotal randomized clinical trials: the public National Lung Screening Trial (NLST) and the Dutch-Belgian Lung Cancer Screening Trial (NELSON) [28]. It can be seen that LDCT is effective in diagnosing lung cancer and reducing its mortality, which has become an evidence-based reality [24]. Some studies have combined LDCT with other lung cancer screening techniques, such as the study conducted by Pastorino et al., who combined LDCT with blood microRNAs (miRNAs) testing to enhance the accuracy of early screening [29]. However, LDCT also has some disadvantages, for instance, it involves radiation exposure and high false-positive rates, Furthermore, LDCT can lead to over-diagnosis and over-treatment due to a high detection rate [8, 9, 30, 31]. Therefore, there are still numerous challenges in applying LDCT for lung cancer screening. These challenges include determining the specific populations that should undergo LDCT screening, establishing appropriate screening intervals to optimize the balance between benefits and risks, and developing specific models to assess which types of lung imaging features are likely to progress into lung cancer. Addressing these scientific problems is imperative for future research.

Magnetic resonance imaging (MRI)

MRI is a non-invasive and radiation-free imaging technique that can provide morphological and functional information about tumors [32]. It has been reported that MRI has a high resolution of soft tissues, which can not only show the morphological characteristics of the diseased issues but also accurately identify the spectrum of the diseased issues and their spatial relationship with the adjacent tissues, especially the surrounding vasculature [33]. Consequently, MRI demonstrates significant value in identifying the lesion sites, differentiating the benign and malignant lesions, classifying the pathological subtypes, identifying the tumor stage and metastasis, and evaluating the therapeutic efficacy [34–36]. MRI demonstrates high sensitivity and specificity in detecting small solid nodules. However, its efficacy is limited in identifying certain sub-solid and pure ground-glass nodules [37]. The diagnostic efficacy of MRI and LDCT has no difference, except for emphysema or pulmonary bulla, bronchiectasis, and reticular opacities [38]. The pulmonary density is relatively low due to the lung tissue containing gas, which leads to weak signal intensity in MRI [39]. Consequently, MRI is rarely used for the assessment of respiratory diseases. Furthermore, the sensitivity of MRI in detecting small lesions within lung tissue is superior to that of LDCT, which indicates that MRI serves as a valuable complement to the LDCT in evaluating unknown pulmonary masses [40].

Positron emission tomography-computed tomography (PET-CT)

PET-CT is an advanced medical imaging technology that integrates PET and CT technology, and is presently

considered as an optimal functional molecular imaging technique for diagnosing lung cancer. This approach enables the integration of anatomical imaging with metabolic functional imaging of tissues, thereby providing comprehensive information for the physiology, pathology, and biochemical metabolism of the tissue [41, 42]. Sun et al. demonstrated that PET-CT exhibits a high specificity of 89% and a sensitivity of 70% in distinguishing benign and malignant lung tumors [42]. In a word, PET-CT can not only show the primary lesion of the tumors but also detect metastatic lesions through hematogenous or lymphatic pathways, which contributes to identifying the pathological nature and stage of the tumor [43]. Tumor tissue exhibits vigorous metabolic activity, particularly characterized by an elevated rate of glycolytic process [44, 45]. Therefore, metabolic imaging is one of the most sensitive methods for the early diagnosis of malignant tumors. PET-CT indicates that the tumor is malignant when it demonstrates increased metabolic activity; conversely, the absence of such metabolic elevation may suggest a benign nature [46, 47]. In addition, the metabolic information obtained from PET-CT can provide critical guidance in selecting optimal sites for lesion biopsy [48]. However, PET-CT has some limitations, such as its high cost, susceptibility to respiratory motion artifacts, and fluorodeoxyglucose (FDG) metabolism not exclusive to tumor cells, resulting in a high false-positive rate [49]. Therefore, PET-CT is not recommended for routine early lung cancer screening in large populations.

Pathological examination

Pathological examination was regarded as a "gold standard" for lung cancer diagnosis and can be divided into cytological examination and histological biopsy [50, 51]. Cytological examination primarily involves sputum cytology, whereas histological biopsy includes bronchoscopy biopsy and percutaneous lung aspiration biopsy [51].

Sputum exfoliative cytological examination

Sputum has long been recognized as an ideal medium for early screening of lung cancer. Compared with other invasive screening methods, sputum exfoliative cytological examination has the advantages of easy access and non-invasiveness [52]. It was reported that lung cancer can be diagnosed if cancerous cells are detected in sputum, with sputum cytology being noted for its high specificity [53]. However, the sensitivity of sputum exfoliative cytological examination for early lung cancer screening is limited due to some factors, such as the method of sputum collection, sputum quality, and other variables. Consequently, it has not achieved the anticipated efficacy in clinical application [54]. Currently, most studies on sputum exfoliative cytological examination focus on exploring the clinical efficacy of combining it with other examinations, including AI, to screen early-stage lung cancer comprehensively [52, 55]. It has also been reported that an approach with high accuracy that combines sputum exfoliative cytological examination by flow cytometry and machine learning techniques for diagnosing lung cancer [52]. In the future, it is necessary to further explore how to apply the advantages of sputum exfoliative cytological examination to the early screening of clinical lung cancer.

Bronchoscopic biopsy

Although LDCT screening has shown efficacy in reducing mortality among individuals at high risk for lung cancer, bronchoscopic biopsy exhibits significantly greater sensitivity, exceeding 95%, in diagnosing early-stage central lung cancer [49, 56]. Consequently, bronchoscopic biopsy is considered as an optimal screening tool for the early detection of central lung cancer. Bronchoscopy encompasses conventional White Light Bronchoscopy (WLB), and newly developed bronchoscopic techniques such as Autofluorescence Bronchoscopy (AFB) and Narrow-Band Imaging (NBI). Compared with ordinary WLB, AFB and NBI can significantly improve the accuracy and sensitivity of diagnosis [57, 58]. Particularly, AFB exhibits superior sensitivity in the detection of hyperplasia and chemosis compared to sputum cytology. Numerous studies reported that AFB can be effectively utilized in high-risk patients regardless of sputum cytology outcomes [53]. However, AFB has not been widely accepted, primarily due to the necessity for special equipment and the high cost [59]. NBI demonstrates superior efficacy compared to WLB in detecting early-stage and invasive lung cancer [49]. This research datum shows that NBI holds greater potential for development in the early detection of lung cancer. Some studies have also found that Transbronchial Needle Aspiration (TBNA) significantly enhances the detection rate of lung cancer [60]. However, this technique primarily utilizes suction-generated negative pressure to obtain tissue samples, which may exacerbate local tissue damage and carries a potential risk of concurrent infection [61]. Consequently, implementing bronchoscopic biopsy for the early screening of lung cancer on a large scale remains challenging in practical applications.

Ultrasound or CT-guided percutaneous lung aspiration biopsy

Ultrasound or CT-guided percutaneous lung aspiration biopsy, currently recognized as the "gold standard" for determining the benign or malignant characteristics of lung masses, is primarily utilized to diagnose advanced-stage lung cancer [11]. However, the puncture is an invasive

examination, and tumor heterogeneity exists within and between tumors, which leads to poor reproducibility of results [51]. Additionally, puncture may also induce serious complications, such as hemorrhage and pneumothorax, making it difficult to apply for early screening of clinical lung cancer [62–64]. Numerous researchers are still exploring the factors contributing to serious complications induced by puncture and seeking the optimal solution to enhance the clinical value of this technique [12, 65]. In summary, percutaneous lung aspiration biopsy is mainly used for diagnosing advanced-stage lung cancer; however, its application in large-scale early lung cancer screening continues to present challenges.

Commonly used serum diagnostic marker in clinical practice

Imaging examinations have limitations such as high false-positive rates and over-diagnosis, while pathological biopsies are invasive, rendering them unsuitable for screening in large populations [8, 60, 66]. In contrast, liquid biopsy is a non-invasive alternative that can identify cancer-related biomarkers in peripheral blood and can be performed repeatedly at multiple time points, with the potential to determine spatiotemporal heterogeneity [67]. The detection of commonly used serum tumor markers and seven TAAbs are crucial assistive technique for early lung cancer screening in clinical practice. When integrated with the LDCT, these approaches can increase the accuracy of early-stage lung cancer screening [68, 69].

Serum tumor markers

Serum tumor markers are relatively specific substances produced by tumor cells [70]. Elevated expression levels of tumor markers may partially indicate the presence of tumors within the body and serve as valuable observational indicators for evaluating therapeutic efficacy and prognostic outcomes [13]. At present, the serum tumor markers of lung cancer routinely detected in clinical practice primarily include Cytokeratin-19 Fragment Antigen 21-1 (CYFRA 21-1), Carcinoembryonic Antigen (CEA), Neuron-Specific Enolase (NSE), Carbohydrate Antigen-199 (CA-199), and Squamous Cell Carcinoma-Associated Antigen (SCC-A) [71–74]. CEA, a surface glycoprotein involved in cell adhesion processes, is a commonly used biomarker for lung cancer, especially lung adenocarcinoma. However, its diagnostic specificity is limited, as elevated CEA levels may also be observed in colorectal cancer, breast cancer, and benign lung tumors [75]. CYFRA21-1, a keratin intermediate filament protein, is a critical component of the eukaryotic cytoskeleton. Elevated levels of CYFRA21-1 can reflect tumor necrosis caused by aggressive growth and are associated with poor survival rates [71]. NSE is a glycolytic enzyme that is predominantly expressed in neuroendocrine tumors, including small-cell lung cancer and large-cell neuroendocrine carcinoma. Elevated levels of NSE may display the neuroendocrine characteristics of lung cancer [71]. CA-199 is mainly utilized for the diagnosis and treatment of pancreatic cancer; in addition, its levels are frequently elevated in cases of lung cancer. The elevated concentration of CA-199 may indicate the progression of lung cancer [71]. SCCA is a tumor marker used to monitor squamous cell carcinoma and plays an important role in the diagnosis and treatment of lung squamous cell carcinoma [76, 77]. Individual tumor markers exhibit limited specificity in diagnosing lung cancer, and early lung cancer screening can be performed by combining the detection of multiple lung cancer serum markers. Compared with other alternative screening methods, combined detection of numerous lung cancer serum markers has advantages such as low cost, high sensitivity, and greater patient acceptance [78]. In contrast with Alpha-Fetoprotein (AFP), which functions as a specific serum biomarker for hepatocellular carcinoma, no specific serum biomarker for early lung cancer screening currently exists [79, 80]. Consequently, identifying and developing precise serum markers for lung cancer holds significant prospects in early lung cancer screening.

Seven tumor-associated antigen autoantibodies (TAAbs)

TAAbs, which exist in the bloodstream, are immunoglobulins synthesized by the immune system in response to specific antigens expressed on tumor cells. TAAb can be identified after being released into the circulatory peripheral blood [81]. The common seven TAAbs include Tumor Suppressor Gene p53 (p53), Protein Gene Product 9.5 (PGP9.5), Sex-Determining Region Y Box2 (SOX2), Globoside Binding Unit 4-5 (GBU4-5), Melanoma Antigen A1 (MAGE A1), Cancer-Associated Gene (CAGE), and G Antigen 7 (GAGE7) [69, 82–84]. TAAbs have the following characteristics: They already exist before imaging diagnosis; their levels are significantly elevated in patients with lung cancer compared to healthy individuals; they possess a long half-life and remain stable in serum [85–88]. However, the use of a single TAAb alone is insufficient for the accurate screening of early-stage lung cancer. Interestingly, the sensitivity of the combined detection of seven TAAbs is much higher than that of a single TAAb detection, indicating that the combined detection of TAAbs holds substantial clinical value and prospects for early lung cancer screening [86]. In addition, a large number of studies have revealed that the combination detection of seven TAAbs and LDCT significantly enhances the sensitivity for early screening of lung cancer

[69]. Nevertheless, the elevated false-positive rate associated with LDCT warrants further consideration [14]. Therefore, it is imperative to investigate a detection methodology that is more compatible with the integrated detection of the seven TAAbs and has higher accuracy in the future applications.

Research advances in novel liquid biopsy approaches

Current methodologies for early lung cancer screening exhibit certain limitations in practical application. Recent studies have increasingly employed liquid biopsy techniques to identify effective biomarkers for the early detection of lung cancer [15, 89]. Liquid biopsy techniques, including Circulating Tumor Cells (CTCs), Cell-Free DNA (cfDNA), exosomes, and DNA methylation, are increasingly gaining prominence [2]. These liquid biopsy approaches provide comprehensive information into the genomic, transcriptomic, and proteomic landscapes of tumors, thereby playing pivotal roles in early diagnosis and therapeutic strategies [15].

Circulating tumor cells (CTCs)

CTCs are neoplastic cells derived from either the primary tumor or metastatic sites and subsequently enter the circulatory system [90]. In healthy individuals, CTCs barely exist in the bloodstream. In contrast, patients with solid tumors exhibit approximately one CTC per 10^6–10^7 leukocytes [91]. The morphology of CTCs is similar to that of primary tumor cells. Nonetheless, CTCs possess the Epithelial–Mesenchymal Transition (EMT) characteristic, facilitating their dissociation from the primary tumor site and entry into the periphery bloodstream, subsequently forming secondary tumors at new metastatic sites [92]. Therefore, the capture of CTCs holds significant importance for the early diagnosis of cancer [93]. Nevertheless, the content of CTCs is extremely low in peripheral blood, and it is challenging to separate CTCs from many circulating peripheral blood cells directly [94]. Traditional CTC separation technologies have been significantly impacted by challenges such as cell viability and fragility, leading to poor separation efficacy. But the recent breakthroughs in the molecular/morphology/immunology-based characterization of CTCs aim at cancer precision medicine through a "virtual and a real-time biopsy," empowering them to be a minimally-manipulated ones for cancer clinical research [95]. With the continuous innovation and improvement of current separation technologies, CTCs are expected to serve as predictive biomarkers for practical early screening of lung cancer in clinical settings in the near future.

Circulating free DNA (cfDNA)

cfDNA refers to DNA fragments released by cancer cells during apoptosis, necrosis, or active secretion of cancer cells, and is widely present in body fluids such as peripheral blood and urine [89, 96]. It has been reported that the content of cfDNA in the serum of patients with tumors, including lung cancer, is markedly elevated compared to that in healthy individuals [97, 98]. The detection of cfDNA is non-invasive and exhibits high sensitivity, making it a promising biomarker for early lung cancer screening [99]. The primary techniques for cfDNA detection include Polymerase Chain Reaction (PCR) and Next-Generation Sequencing (NGS), with NGS being particularly noted for its high sensitivity and large throughput, thus establishing it as an effective analytical method [100]. In addition to evaluating the fundamental information of cfDNA, including concentration, integrity, and fragment length, the current study also assessed the methylation level of cfDNA, which provides clues for early screening of lung cancer by comparing the cfDNA profiles between lung cancer patients and a healthy control group [101–103]. The sensitivity of cfDNA testing is influenced by various pre-analytic and post-analytic factors. Current studies often fail to adequately control pre-analytical variables, resulting in a lack of reliability. Addressing this issue is essential for extending the application of cfDNA testing to clinical screening [104].

Exosomes

Exosomes are intracellular vesicles ranging from 30 to 150 nm in size, secreted by various cell types, and widely exist in numerous body fluids, including plasma, saliva, urine, breast milk, and so on [105]. These vesicles carry specific biological information, such as proteins, lipids, DNA, and RNA (mRNA and non-coding RNA), and play an important role in intercellular communication processes [106–108]. KHAN et al. found that the contents of Lung Cancer Cells-Derived Exosomes (LCCDE) differed from those of healthy individuals, and the exosomes present in the peripheral blood of lung cancer patients exhibited elevated expression levels of various miRNAs [106]. In addition, LCCDE can modulate the tumor micro environment and the physiological functions of adjacent tissue cells, thereby influencing the progression and metastasis of lung cancer. These exosomes can also regulate the anti-tumor immune response to help cancer cells evade the host immune system [109–111]. The above studies indicate that LCCDE represents a promising candidate biomarker for lung cancer screening and prognosis. Moreover, exosomes are stable and have vesicle-coating properties, which may serve as drug delivery carriers, thereby expanding the prospects for their application in lung cancer treatment [49]. Nevertheless, the

efficient extraction and purification of exosomes remain challenging due to their nanometer-scale size, it needs to be further solved in the future [112].

DNA methylation

DNA methylation refers to the Methyl Group (CH_3) covalently integrated into the C-5 position of cytosine within Cytosine–Phosphate–Guanine (CpG) dinucleotides in the genomic DNA by DNA Methyltransferase (DNMT) [113]. DNA methylation is a prevalent epigenetic modification, and dysregulation of DNA methylation is implicated in the pathogenesis of numerous diseases, notably cancer [114]. Among them, high methylation levels of tumor suppressor genes or low methylation levels of oncogenes are important to promote tumor occurrence and development [115]. Therefore, analyzing the abnormal DNA methylation levels of tumor suppressor genes or oncogenes may provide valuable information for early lung cancer screening. For instance, Liang W et al. developed a diagnostic model based on DNA methylation sequencing to identify patients with pulmonary nodules, and the results showed that DNA methylation analysis was superior to PET-CT in distinguishing between benign and malignant pulmonary nodules [116]. Non-invasive DNA methylation detection holds significant potential for clinical benefits and may develop as an effective early diagnostic tool for lung cancer in the future [117]. However, the absence of standardized detection methodologies for DNA methylation is a limiting factor in its application for early screening and diagnosis of lung cancer [118]. This issue needs to be further addressed in the future.

Other liquid biopsy components

In addition to the aforementioned novel markers, numerous other potentially valuable liquid biopsy components have also been studied in recent years. These include miRNAs, which can regulate the expression of specific target genes; Long Non-Coding RNAs (lncRNAs), which can influence epigenetic and post-transcriptional regulation; Circular RNAs (circRNAs), which can regulate gene expression at the pre-transcriptional, post-transcriptional, and translational levels [119–121]. Non-coding RNAs such as miRNAs, lncRNAs, and circRNAs are widely present in various body fluids in the human body and are easily accessible and non-invasive. They can affect the proliferation and metastasis of tumor cells through multiple pathways [70]. Numerous studies have shown that these liquid biopsy components possess significant diagnostic potential for lung cancer, whether used independently or in combination with other detection techniques, they hold considerable prospects for early lung cancer screening [2, 122, 123]. However, due to the inherent instability of RNA in blood and its rapid degradation by RNases present in the bloodstream or external environment, developing techniques to preserve its stability over extended periods remains a significant challenge that needs further addressing [124].

Artificial intelligence (AI)

AI is a branch of computer science that includes research in robotics, language recognition, image recognition, natural language processing, and expert systems [125]. AI algorithms, including Natural Language Processing (NLP), machine learning, deep learning, and reinforcement learning, play an important role in lung cancer imaging [126, 127]. Pulmonary nodules are frequently identified during physical examinations. Although most lung nodules are benign, the incidence of early-stage malignant lung tumors remains substantial, particularly for lung nodules exceeding 3 cm in diameter [128, 129]. Radiologists should accurately distinguish benign and malignant nodules after detecting them by imaging examination, and provide strategies for the subsequent treatment. However, identifying benign and malignant nodules usually relies on pathological examination. Recent literature has reported that AI can quickly locate suspicious nodules and provide accurate diagnostics, thereby reducing misdiagnoses and missed diagnoses [16, 130]. Various Computer-Aided Diagnosis (CAD) tools have been developed to assist radiologists in the early detection and identification of suspicious nodules, as well as in the assessment of their malignancy [126, 131, 132]. Several studies have indicated that radiologists exhibit a true-positive rate of 46.53% in detecting pulmonary nodules via CT scans, which is lower than 98.54% by combining CT and AI technology. The discrepancy is primarily attributed to the fact that radiologists could miss certain micro-nodules and atypical nodules in the lung [133]. Therefore, AI can contribute to elevating the true-positive rate of lung nodule diagnosis.

Furthermore, AI facilitates the pathological classification of lung cancer. Still, there are some limitations in the application of AI in pathology, such as the lack of standardized procedures for specimen handling and slide staining, as well as the absence of an authoritative lung cancer pathological image database, these deficiencies may adversely affect the diagnostic accuracy of AI systems [126]. In addition, in terms of explainability, AI is deficient in conducting comprehensive outcomes analyses and cannot explain precise disease mechanisms like a specialist doctor [27, 126]. Consequently, significant advancements are required before AI technology can fully replace medical professionals. In a word, AI technology has improved the efficiency of early screening and diagnosis of lung cancer and presents promising potential applications in the future.

Imaging examination (including CXR, LDCT, MRI, and PET-CT) and pathological examination (including sputum exfoliative cytological examination, bronchoscopic biopsy, ultrasound or CT-guided percutaneous lung aspiration biopsy) are depicted in Fig. 1. Commonly used serum tumor markers (such as CYFRA 21-1, CEA, NSE, CA-199, and SCC-A) and TAAbs are shown in Fig. 2. Novel liquid biopsy methods (such as CTCs, cfDNA, exosomes, and DNA methylation alteration), as well as the characteristics of AI, are also depicted in Fig. 2. Table 1 summarizes and lists the advantages and disadvantages of the above screening techniques.

Discussion

Compared with existing reviews on early lung cancer screening, this review systematically outlines the limitations of traditional technologies, including imaging examinations (e.g., LDCT and PET-CT), tissue biopsies (e.g., bronchoscopy and TBNA), and conventional tumor markers, while focusing on the "high invasion and low accuracy" technical bottleneck. We deeply analyze the breakthrough progress of novel liquid biopsy technologies (e.g., cfDNA and DNA methylation testing) in non-invasiveness and diagnostic efficacy. The review also demonstrates that novel liquid biopsies, such as capturing circulating tumor components, can enhance sensitivity compared to traditional screen technologies, while

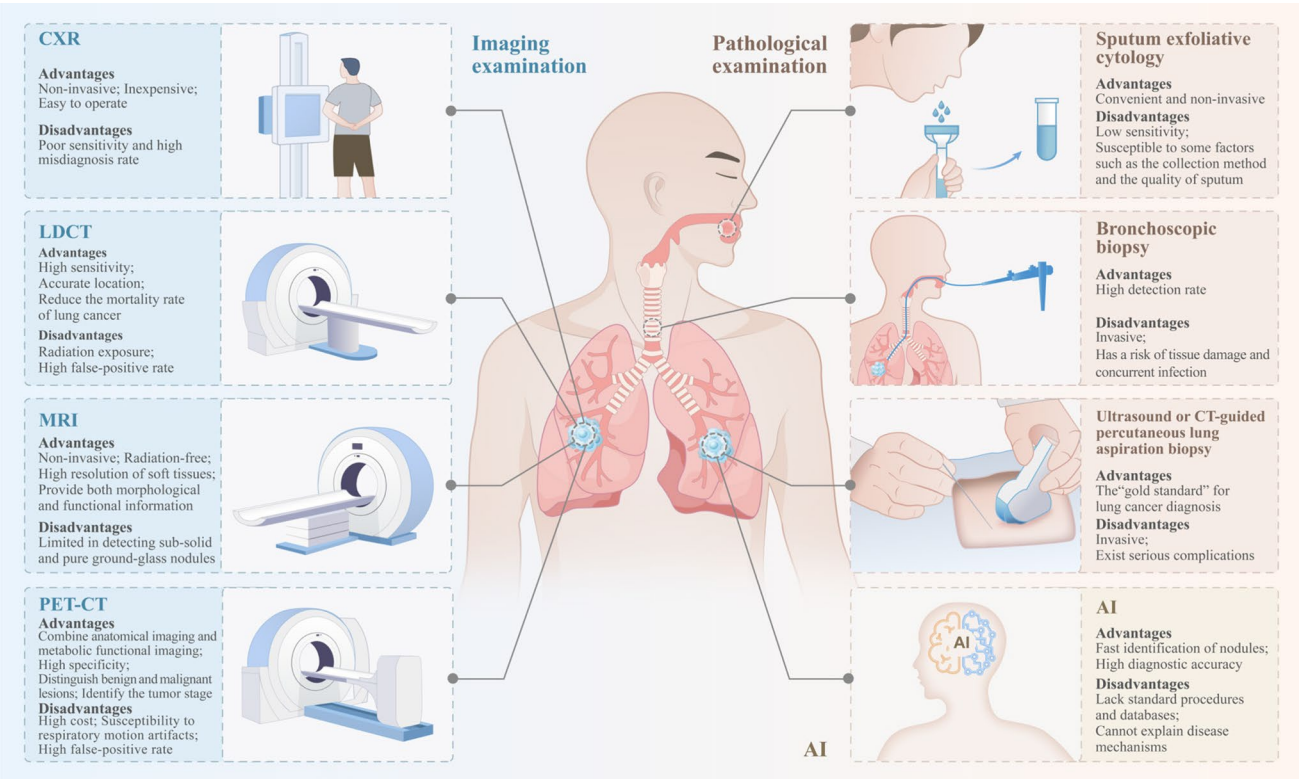

Fig. 1 Imaging examination, pathological examination, and AI for lung cancer screening techniques. The figure depicts two types of traditional lung cancer screening technologies: imaging examination and pathological examination. Imaging examination is important for diagnosing lung diseases, and it mainly includes CXR, LDCT, MRI, and PET-CT. Among them, CXR has the advantages of being non-invasive, inexpensive, and easy to operate, but it has poor sensitivity and a high misdiagnosis rate. LDCT, the most commonly used imaging method for early lung cancer screening, can reduce the mortality rate of lung cancer. However, LDCT also causes radiation exposure and a high false-positive rate, so the high-risk group of lung cancer should be identified before LDCT application. MRI is non-invasive and radiation-free; it can provide both morphological and functional information about tumors and has a high resolution of soft tissues. PET-CT enables the integration of anatomical imaging with metabolic functional imaging of tissues, thereby providing comprehensive information for the physiology, pathology, and biochemical metabolism of the tissue. Meanwhile, PET-CT has some limitations, such as its high cost, susceptibility to respiratory motion artifacts, and high false-positive rate. Pathological examination can be divided into sputum exfoliative cytology, bronchoscopic biopsy, and ultrasound or CT-guided percutaneous lung aspiration biopsy. Among them, sputum exfoliative cytology is convenient and non-invasive. The ultrasound or CT-guided percutaneous lung aspiration biopsy is the “gold standard” for determining benign or malignant characteristics of lung masses. Still, it is invasive, similar to the bronchoscopic biopsy, which may exacerbate tissue damage at the biopsy site and carry a risk of concurrent infection

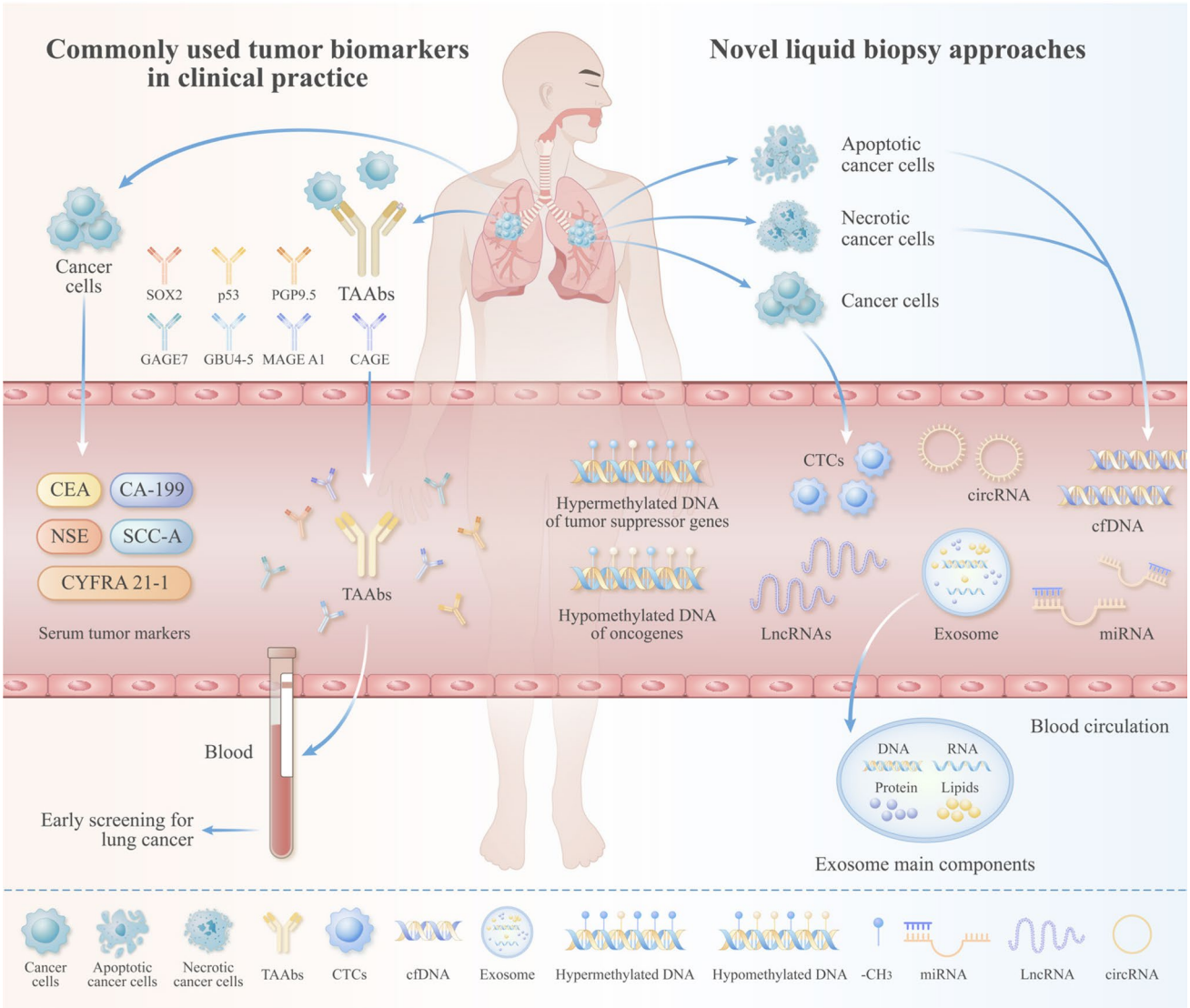

Fig. 2 The commonly used serum tumor markers, TAAbs, and novel liquid biopsy markers for lung cancer screening techniques. This figure summarizes the commonly used serum tumor markers, TAAbs, and novel liquid biopsy markers. The left part of the figure shows the commonly used clinical tumor biomarkers and seven types of TAAbs. The serum markers that are routinely detected for lung cancer include CYFRA 21-1, CEA, NSE, CA-199, and SCC-A. Early lung cancer screening can be performed by the combined detection of multiple lung cancer serum markers, with some advantages such as low cost, high sensitivity, and greater patient acceptance. TAAbs are immunoglobulins produced by the immune system in response to specific antigens expressed on tumor cells, which possess a long half-life and remain stable in the serum. Seven types of TAAbs include p53, PGP9.5, SOX2, GAGE7, GBU4-5, MAGE A1, and CAGE. Combined detection of TAAbs holds substantial clinical value and prospects for early lung cancer screening. The right part of the figure shows novel liquid biopsy markers, mainly including CTCs, cfDNA, and exosomes, as well as hypermethylation of tumor suppressor genes or hypomethylation of oncogenes. Among them, CTCs are tumor cells that are shed from primary tumors or metastatic sites and enter into the blood circulation, and they are almost absent in healthy individuals. cfDNA is a DNA fragment released by cancer cells during apoptosis, necrosis, or active secretion of cancer cells, and cfDNA is widely present in human body fluids, such as blood, urine, and so on. Exosomes are intracellular vesicles carrying specific biological information such as protein, lipids, DNA, RNA, etc. The contents of exosomes derived from lung cancer cells are significantly different from those of normal individuals; DNA methylation disorders, such as hypermethylation of tumor suppressor genes or hypomethylation of oncogenes, play a critical role in cancer progression and provide effective information for early lung cancer screening. In addition to the aforementioned novel markers, numerous other potentially valuable liquid biopsy components such as miRNAs, lncRNAs, and circRNAs also played significant roles in early lung cancer screening. The above liquid biopsy components show significant potential and may be suitable for widespread screening in large populations

Table 1 The advantages and disadvantages of the lung cancer screening methods

Screening methods	Advantages	Disadvantages	References
CXR	Non-invasive; Inexpensive; Easy to operate	Poor imaging; Poor sensitivity; High misdiagnosis rate	[17, 18, 22]
LDCT	High sensitivity; Accurate location; Distinguish benign and malignant lesions	Radiation exposure; High false-positive rates	[8, 9, 18, 23–27, 30, 31]
MRI	Non-invasive; Radiation-free; High resolution of soft tissues; Provide morphological and functional information about tumors	Limited in detecting sub-solid and pure ground-glass nodules	[32–37]
PET-CT	Combine anatomical imaging and metabolic functional imaging; High specificity; Distinguish benign and malignant lesions; Identify the tumor stage; Provide guidance for lesion biopsy	High cost; Motion artifacts; High false positives	[41–49]
Sputum exfoliative cytological examination	Easy to obtain; Non-invasiveness; High specificity	Low sensitivity; Susceptible to some factors, such as the collection method and quality of sputum	[52–54]
Bronchoscopic biopsy	High detection rate; Greater sensitivity in diagnosing central lung cancer	Has a risk of tissue damage and infection	[49, 56–58, 61]
Ultrasound or CT-guided percutaneous lung aspiration biopsy	The "gold standard" for diagnosing lung cancer	Invasive; Existing serious complications such as hemorrhage and pneumothorax	[11, 62, 63, 71–74, 79, 8051]
Serum tumor markers	Non-invasive; Repeatable; High sensitivity; Acceptable	Poor specificity of a single tumor marker	[69]
TAAbs	Non-invasive; Repeatable; High sensitivity; Acceptable; Long half-life and stable	Low sensitivity of single TAAb	[81, 85, 88]
CTCs	Non-invasive; Repeatable; High sensitivity; CTCs barely exist in the blood of healthy individuals	Lacking suitable methods for CTCs enrichment and separation	[88, 91–95]
cfDNA	Non-invasive; Repeatable; High sensitivity; Can be markedly elevated in the serum	The detection reliability remains to be enhanced	[89, 97–103]
Exosome	Non-invasive; Repeatable; High sensitivity; Carry specific biological information	Hard to efficiently extract and purify exosomes	[49, 105–108]
DNA methylation	DNA methylation was superior to PET-CT in distinguishing between benign and malignant pulmonary nodules	Lacking standardized detection methods for DNA methylation	[116, 118]
Other liquid biopsy components: miRNA, lncRNAs, and circRNA	Non-invasive; Accessible; High sensitivity	Unstable and easily degraded rapidly by RNases	[70, 119, 124]
AI	Fast identification of nodules; High diagnostic accuracy	Lacking standard procedures and databases; Cannot explain disease mechanisms like a specialist	[16, 27, 126]

avoiding the complications of needle biopsies. Furthermore, this review provides a novel integration of AI-assisted diagnostic applications, emphasizing that deep learning techniques applied to imaging features can effectively reduce the false-positive rate of LDCT. Unlike previous reviews that merely list screening technologies, this study further proposes three development strategies: A liquid biopsy-based pre-screening model incorporating risk factors such as age and smoking history, which can reduce excessive imaging examination in healthy populations; a "imaging-AI-liquid biopsy" laddered workflow integrated with liquid biopsy can improve diagnostic efficiency; and the development of standardized biomarker panels (e.g., cfDNA combined with DNA methylation profiles). These strategies are expected to surpass the limitations of the traditional single screening technique and provide molecular-level evidence for personalized screening. More importantly, the optimized strategies of combining traditional screening methods with emerging technologies not only offer theoretical guidance for constructing precise clinical screening models but also pave a new path for early lung cancer diagnosis. Of course, this review also has some limitations, mainly in that the proposed comprehensive screening model of "imaging-AI-liquid biopsy" has not been validated by large-scale clinical practice, and its applicability and operability in different medical environments need further exploration. In the future, we will pay attention to and carry out prospective clinical studies to provide sufficient evidence for optimizing the early lung cancer screening strategy.

Conclusion and perspective

The high mortality rate of lung cancer urgently demands a breakthrough in current screening technologies to overcome the bottleneck of “high invasiveness yet low accuracy”. This systematic review demonstrates that conventional screening methods, including imaging (e.g., LDCT), tissue biopsies, and serum tumor biomarkers, have significant limitations. In contrast, emerging liquid biopsy techniques (e.g., cfDNA and DNA methylation assays) offer a non-invasive approach with superior diagnostic performance, exhibiting higher sensitivity than traditional serum biomarkers while eliminating the risks associated with invasive procedures. The integration of AI-assisted diagnostics further optimizes screening protocols. AI can utilize deep learning to analyze imaging features, then reduce LDCT false-positive rates and significantly improve the distinction between benign and malignant nodules. The strategic combination of conventional and novel technologies can facilitate constructing a precise and efficient screening framework, which not only minimizes unnecessary examination and radiation exposure in healthy populations but also enables personalized screening through molecular-level profiling. To translate these advancements into clinical practice, future efforts must prioritize interdisciplinary collaboration (among clinical oncologists, personalized medicine specialists, cellular and molecular medicine specialists, and so on) and large-scale clinical validation. These actions will accelerate the implementation of these innovative strategies, ultimately enhancing early lung cancer detection rates, improving patient outcomes. This review provides a critical theoretical foundation for technological innovation in lung cancer screening.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
2. Ren F, Fei Q, Qiu K, Zhang Y, Zhang H, Sun L. Liquid biopsy techniques and lung cancer: diagnosis, monitoring and evaluation. J Exp Clin Cancer Res. 2024;43(1):96. https://doi.org/10.1186/s13046-024-03026-7.

3. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63. https://doi.org/10.3322/caac.21834.
4. Bidard FC, Kiavue N, Jacot W, et al. Overall survival with circulating tumor cell count-driven choice of therapy in advanced breast cancer: a randomized trial. J Clin Oncol. 2024;42(4):383–9. https://doi.org/10.1200/jco.23.00456.
5. Wu JT, Wakelee HA, Han SS. Optimizing lung cancer screening with risk prediction: current challenges and the emerging role of biomarkers. J Clin Oncol. 2023;41(27):4341–7. https://doi.org/10.1200/jco.23.01060.
6. Zeng H, Ran X, An L, et al. Disparities in stage at diagnosis for five common cancers in China: a multicentre, hospital-based, observational study. Lancet Public Health. 2021;6(12):e877–87. https://doi.org/10.1016/s2468-2667(21)00157-2.
7. Bi JH, Tuo JY, Xiao YX, et al. Observed and relative survival trends of lung cancer: a systematic review of population-based cancer registration data. Thorac Cancer. 2024;15(2):142–51. https://doi.org/10.1111/1759-7714.15170.
8. Jonas DE, Reuland DS, Reddy SM, et al. Screening for lung cancer with low-dose computed tomography: updated evidence report and systematic review for the us preventive services task force. JAMA. 2021;325(10):971–87. https://doi.org/10.1001/jama.2021.0377.
9. Lung cancer incidence and mortality with extended follow-up in the national lung screening trial. J Thorac Oncol. 2019;14(10):1732–42. https://doi.org/10.1016/j.jtho.2019.05.044.
10. Ledda RE, Funk G-C, Sverzellati N. The pros and cons of lung cancer screening. Eur Radiol. 2025;35(1):267–75. https://doi.org/10.1007/s00330-024-10939-6.
11. D'Agnano V, Perrotta F, Stella GM, et al. Molecular diagnostic yield and safety profile of ultrasound-guided lung biopsies: a cross-sectional study. Cancers (Basel). 2024;16(16):2860. https://doi.org/10.3390/cancers16162860.
12. He C, Zhao L, Yu HL, et al. Pneumothorax after percutaneous CT-guided lung nodule biopsy: a prospective, multicenter study. Quant Imaging Med Surg. 2024;14(1):208–18. https://doi.org/10.21037/qims-23-891.
13. Zhang Z, Yuan F, Chen R, et al. Dynamics of serum tumor markers can serve as a prognostic biomarker for Chinese advanced non-small cell lung cancer patients treated with immune checkpoint inhibitors. Front Immunol. 2020;11:1173. https://doi.org/10.3389/fimmu.2020.01173.
14. Li W, Liu JB, Hou LK, et al. Liquid biopsy in lung cancer: significance in diagnostics, prediction, and treatment monitoring. Mol Cancer. 2022;21(1):25. https://doi.org/10.1186/s12943-022-01505-z.
15. Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat Rev Genet. 2019;20(2):71–88. https://doi.org/10.1038/s41576-018-0071-5.
16. Kanan M, Alharbi H, Alotaibi N, et al. Ai-driven models for diagnosing and predicting outcomes in lung cancer: a systematic review and meta-analysis. Cancers (Basel). 2024;16(3): 674. https://doi.org/10.3390/cancers16030674.
17. Fan W, Yang Y, Qi J, et al. A deep-learning-based framework for identifying and localizing multiple abnormalities and assessing cardiomegaly in chest X-ray. Nat Commun. 2024;15(1):1347. https://doi.org/10.1038/s41467-024-45599-z.
18. Gefter WB, Hatabu H. Reducing errors resulting from commonly missed chest radiography findings. Chest. 2022;163(3):634–49. https://doi.org/10.1016/j.chest.2022.12.003
19. Kiruthika K, Khilar R. RETRACTED ARTICLE: Segmentation of lung on CXR images based on CXR-auto encoder segmentation with MRF. Opt Quant Electron. 2024;56(4):673. https://doi.org/10.1007/s11082-024-06507-3.
20. Bradley SH, Bhartia BS, Callister ME, et al. Chest X-ray sensitivity and lung cancer outcomes: a retrospective observational study. Br J Gen Pract. 2021;71(712):e862–8. https://doi.org/10.3399/bjgp.2020.1099.
21. Sachithanandan A, Lockman H, Azman RR, Tho LM, Ban EZ, Ramon V. The potential role of artificial intelligence-assisted chest X-ray imaging in detecting early-stage lung cancer in the community-a proposed algorithm for lung cancer screening in Malaysia. Med J Malaysia. 2024;79(1):9–14.
22. Kwak SH, Kim KY, Choi JS, et al. Impact of AI-assisted CXR analysis in detecting incidental lung nodules and lung cancers in non-respiratory outpatient clinics. Front Med (Lausanne). 2024;11:1449537. https://doi.org/10.3389/fmed.2024.1449537.
23. Marmor HN, Zorn JT, Deppen SA, Massion PP, Grogan EL. Biomarkers in lung cancer screening: a narrative review. Curr Chall Thorac Surg. 2023;5:5. https://doi.org/10.21037/ccts-20-171.
24. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction—evidence, pitfalls and future perspectives. Nat Rev Clin Oncol. 2021;18(3):135–51. https://doi.org/10.1038/s41571-020-00432-6.
25. Wei B, Wu F, Xing W, et al. A panel of DNA methylation biomarkers for detection and improving diagnostic efficiency of lung cancer. Sci Rep. 2021;11(1):16782. https://doi.org/10.1038/s41598-021-96242-6.
26. Li C, Wang H, Jiang Y, et al. Advances in lung cancer screening and early detection. Cancer Biol Med. 2022;19(5):591–608. https://doi.org/10.20892/j.issn.2095-3941.2021.0690.
27. Loh HW, Ooi CP, Seoni S, Barua PD, Molinari F, Acharya UR. Application of explainable artificial intelligence for healthcare: a systematic review of the last decade (2011–2022). Comput Methods Programs Biomed. 2022;226: 107161. https://doi.org/10.1016/j.cmpb.2022.107161.
28. Zyla J, Marczyk M, Prazuch W, et al. Combining low-dose computer-tomography-based radiomics and serum metabolomics for diagnosis of malignant nodules in participants of lung cancer screening studies. Biomolecules. 2023;14(1):44. https://doi.org/10.3390/biom14010044.
29. Pastorino U, Boeri M, Sestini S, et al. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. Ann Oncol. 2022;33(4):395–405. https://doi.org/10.1016/j.annonc.2022.01.008.
30. Li N, Tan F, Chen W, et al. One-off low-dose CT for lung cancer screening in China: a multicentre, population-based, prospective cohort study. Lancet Respir Med. 2022;10(4):378–91. https://doi.org/10.1016/s2213-2600(21)00560-9.
31. Tang Y, Zhao S, Zhou L, et al. A 16-year evaluation of opportunistic lung cancer screening with low-dose CT in China: comparative findings between non-smokers and smokers. BMC Cancer. 2024;24(1):1322. https://doi.org/10.1186/s12885-024-13056-1.
32. Hoffmann E, Masthoff M, Kunz WG, et al. Multiparametric MRI for characterization of the tumour microenvironment. Nat Rev Clin Oncol. 2024;21(6):428–48. https://doi.org/10.1038/s41571-024-00891-1.
33. Goodburn RJ, Philippens MEP, Lefebvre TL, et al. The future of MRI in radiation therapy: challenges and opportunities for the MR community. Magn Reson Med. 2022;88(6):2592–608. https://doi.org/10.1002/mrm.29450.
34. Yan Q, Yi Y, Shen J, et al. Preliminary study of 3 T-MRI native T1-mapping radiomics in differential diagnosis of non-calcified solid pulmonary nodules/masses. Cancer Cell Int. 2021;21(1):539. https://doi.org/10.1186/s12935-021-02195-1.

35. Tang X, Bai G, Wang H, Guo F, Yin H. Elaboration of multiparametric MRI-based radiomics signature for the preoperative quantitative identification of the histological grade in patients with non-small-cell lung cancer. J Magn Reson Imaging. 2022;56(2):579–89. https://doi.org/10.1002/jmri.28051.
36. Ohno Y, Ozawa Y, Koyama H, et al. State of the art MR imaging for lung cancer TNM stage evaluation. Cancers (Basel). 2023;15(3): 950. https://doi.org/10.3390/cancers15030950.
37. Yang B, Gao Y, Lu J, et al. Quantitative analysis of chest MRI images for benign malignant diagnosis of pulmonary solid nodules. Front Oncol. 2023;13:1212608. https://doi.org/10.3389/fonc.2023.1212608.
38. Mascalchi M, Picozzi G, Puliti D, et al. Lung cancer screening with low-dose CT: what we have learned in two decades of ITALUNG and what is yet to be addressed. Diagnostics (Basel). 2023;13(13):2197. https://doi.org/10.3390/diagnostics13132197.
39. Sodhi KS, Bhatia A, Rana P, Mathew JL. Impact of radial percentage K-space filling and signal averaging on native lung MRI image quality in 3D radial UTE acquisition: a pilot study. Acad Radiol. 2023;30(11):2557–65. https://doi.org/10.1016/j.acra.2023.01.029.
40. Meier-Schroers M, Homsi R, Skowasch D, et al. Lung cancer screening with MRI: results of the first screening round. J Cancer Res Clin Oncol. 2018;144(1):117–25. https://doi.org/10.1007/s00432-017-2521-4.
41. Schwenck J, Sonanini D, Cotton JM, et al. Advances in PET imaging of cancer. Nat Rev Cancer. 2023;23(7):474–90. https://doi.org/10.1038/s41568-023-00576-4.
42. Sun Y, Ge X, Niu R, et al. PET/CT radiomics and deep learning in the diagnosis of benign and malignant pulmonary nodules: progress and challenges. Front Oncol. 2024;14:1491762. https://doi.org/10.3389/fonc.2024.1491762.
43. Farwell MD, Gamache RF, Babazada H, et al. CD8-targeted PET imaging of tumor-infiltrating T cells in patients with cancer: a phase I first-in-humans study of (89)Zr-Df-IAB22M2C, a radiolabeled anti-CD8 minibody. J Nucl Med. 2022;63(5):720–6. https://doi.org/10.2967/jnumed.121.262485.
44. Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: still emerging. Cell Metab. 2022;34(3):355–77. https://doi.org/10.1016/j.cmet.2022.01.007.
45. Aime S, Longo DL, Reineri F, Geninatti Crich S. New tools to investigate tumor metabolism by NMR/MRI. J Magn Reson. 2022;338: 107198. https://doi.org/10.1016/j.jmr.2022.107198.
46. Wang L, Tang G, Hu K, et al. Comparison of (68)Ga-FAPI and (18)F-FDG PET/CT in the evaluation of advanced lung cancer. Radiology. 2022;303(1):191–9. https://doi.org/10.1148/radiol.211424.
47. Momcilovic M, Bailey ST, Lee JT, et al. The GSK3 signaling axis regulates adaptive glutamine metabolism in lung squamous cell carcinoma. Cancer Cell. 2018;33(5):905-21.e5. https://doi.org/10.1016/j.ccell.2018.04.002.
48. Malik D, Pant V, Sen I, Thakral P, Das SS, Cb V. The role of PET-CT-guided metabolic biopsies in improving yield of inconclusive anatomical biopsies: a review of 5 years in a teaching hospital. Diagnostics. 2023;13(13): 2221. https://doi.org/10.3390/diagnostics13132221.
49. Ning J, Ge T, Jiang M, et al. Early diagnosis of lung cancer: which is the optimal choice? Aging (Albany NY). 2021;13(4):6214–27. https://doi.org/10.18632/aging.202504.
50. Feng J, Zhang P, Wang D, Li Y, Tan J. New strategies for lung cancer diagnosis and treatment: applications and advances in nanotechnology. Biomark Res. 2024;12(1):136. https://doi.org/10.1186/s40364-024-00686-7.
51. Shafighi S, Geras A, Jurzysta B, et al. Integrative spatial and genomic analysis of tumor heterogeneity with Tumoroscope. Nat Commun. 2024;15(1):9343. https://doi.org/10.1038/s41467-024-53374-3.
52. Lemieux ME, Reveles XT, Rebeles J, et al. Detection of early-stage lung cancer in sputum using automated flow cytometry and machine learning. Respir Res. 2023;24(1):23. https://doi.org/10.1186/s12931-023-02327-3.
53. Wang G, Jin Y, Xiong K, Jin X, Wang L, Li C. Utility of auto fluorescence-guided biopsy in suspected lung cancer patients with bronchial mucosal lesions. Photodiagnosis Photodyn Ther. 2024;46: 104057. https://doi.org/10.1016/j.pdpdt.2024.104057.
54. Ng JKM, Cheung W, Li JJX, Chan KP, Yip WH, Tse GM. Detection of early (T1) lung cancers and lepidic adenocarcinomas in sputum and bronchial cytology. Ann Diagn Pathol. 2023;67:152191. https://doi.org/10.1016/j.anndiagpath.2023.152191.
55. Si H, Du D, Li W, et al. Sputum-based tumor fluid biopsy: isolation and high-throughput single-cell analysis of exfoliated tumor cells for lung cancer diagnosis. Anal Chem. 2021;93(30):10477–86. https://doi.org/10.1021/acs.analchem.1c00833.
56. Bhamani A, Creamer A, Verghese P, et al. Low-dose CT for lung cancer screening in a high-risk population (SUMMIT): a prospective, longitudinal cohort study. Lancet Oncol. 2025;26(5):609–19. https://doi.org/10.1016/s1470-2045(25)00082-8.
57. Wang H, Liu S, Li F, Gao W, Lv N. Autofluorescence bronchoscope diagnosis for lung nodules and masses. Am J Transl Res. 2021;13(7):7775–82.
58. Iftikhar IH, Musani AI. Narrow-band imaging bronchoscopy in the detection of premalignant airway lesions: a meta-analysis of diagnostic test accuracy. Ther Adv Respir Dis. 2015;9(5):207–16. https://doi.org/10.1177/1753465815589698.
59. Sun S, Yang Y, Chen M, et al. Comparison of autofluorescence and white-light bronchoscopies performed with the Evis Lucera Spectrum for the detection of bronchial cancers: a meta-analysis. Transl Lung Cancer Res. 2020;9(1):23–32. https://doi.org/10.21037/tlcr.2020.01.04.
60. Balasubramanian P, Abia-Trujillo D, Barrios-Ruiz A, et al. Diagnostic yield and safety of diagnostic techniques for pulmonary lesions: systematic review, meta-analysis and network meta-analysis. Eur Respir Rev. 2024;33(173):240046. https://doi.org/10.1183/16000617.0046-2024.
61. Sticht F, Malfertheiner MV, Wiest C, Schulz C, Fisser C, Mamilos A. Comparison of transbronchial biopsy techniques using needle and forceps biopsies in lung cancer for molecular diagnostics: a prospective, randomized crossover trial. Transl Cancer Res. 2024;13(5):2464–74. https://doi.org/10.21037/tcr-23-2320.
62. Wang DX, Wang YG, Ding GX, et al. The effectiveness of the puncture channel plugging for reduction of complications after CT-guided percutaneous transthoracic needle biopsy. Sci Rep. 2023;13(1):12318. https://doi.org/10.1038/s41598-023-38915-y.
63. Tongbai T, McDermott S, Kiranantawat N, et al. Non-diagnostic CT-guided percutaneous needle biopsy of the lung: predictive factors and final diagnoses. Korean J Radiol. 2019;20(11):1515–26. https://doi.org/10.3348/kjr.2019.0014.
64. Balasubramanian P, Abia-Trujillo D, Barrios-Ruiz A, et al. Diagnostic yield and safety of diagnostic techniques for pulmonary lesions: systematic review, meta-analysis and network meta-analysis. Eur Respir Rev. 2024;33(173):240046. https://doi.org/10.1183/16000617.0046-2024.
65. Li J, Su L, Liu J, et al. Optical navigation robot-assisted puncture system for accurate lung nodule biopsy: an animal study. Quant Imaging Med Surg. 2023;13(12):7789–801. https://doi.org/10.21037/qims-23-576.
66. Self WH, Courtney DM, McNaughton CD, Wunderink RG, Kline JA. High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications

for diagnosing pneumonia. Am J Emerg Med. 2013;31(2):401–5. https://doi.org/10.1016/j.ajem.2012.08.041.
67. Andrikou K, Rossi T, Verlicchi A, et al. Circulating tumour cells: detection and application in advanced non-small cell lung cancer. Int J Mol Sci. 2023;24(22): 16085. https://doi.org/10.3390/ijms242216085.
68. Wu Z, Wang F, Cao W, et al. Lung cancer risk prediction models based on pulmonary nodules: a systematic review. Thorac Cancer. 2022;13(5):664–77. https://doi.org/10.1111/1759-7714.14333.
69. Ren S, Zhang S, Jiang T, et al. Early detection of lung cancer by using an autoantibody panel in Chinese population. Oncoimmunology. 2018;7(2): e1384108. https://doi.org/10.1080/2162402x.2017.1384108.
70. Chen H, Zou M, Teng D, Hu Y, Zhang J, He W. Profiling the pattern of the human T-cell receptor γδ complementary determinant region 3 repertoire in patients with lung carcinoma via high-throughput sequencing analysis. Cell Mol Immunol. 2019;16(3):250–9. https://doi.org/10.1038/cmi.2017.157.
71. Chen H, Fu F, Zhao Y, et al. The prognostic value of preoperative serum tumor markers in non-small cell lung cancer varies with radiological features and histological types. Front Oncol. 2021;11: 645159. https://doi.org/10.3389/fonc.2021.645159.
72. Sun A. Clinical role of serum tumor markers SCC, NSE, CA 125, CA 19–9, and CYFRA 21-1 in patients with lung cancer. Lab Med. 2023;54(6):638–45. https://doi.org/10.1093/labmed/lmad020.
73. Zheng R, Wu A, Li J, et al. Progress and outlook on electrochemical sensing of lung cancer biomarkers. Molecules. 2024;29(13):3156. https://doi.org/10.3390/molecules29133156.
74. An J, Zhang M, Fu Y, et al. Emerging electrochemical biosensors for lung cancer-associated protein biomarker and miRNA detection. Int J Biol Macromol. 2024;280(Pt 3): 135972. https://doi.org/10.1016/j.ijbiomac.2024.135972.
75. Li Y, Tian X, Gao L, et al. Clinical significance of circulating tumor cells and tumor markers in the diagnosis of lung cancer. Cancer Med. 2019;8(8):3782–92. https://doi.org/10.1002/cam4.2286.
76. Yang J, Zhang X, Yang G, Mi X, Zhang Y, Sui Y. Study on the application value of concurrent chemoradiotherapy and clinical nursing pathway for postoperative patients with esophageal cancer. J Oncol. 2022;2022:2216529. https://doi.org/10.1155/2022/2216529.
77. Chen F, Zhang X. Predictive value of serum SCCA and CYFRA21-1 levels on radiotherapy efficacy and prognosis in patients with non-small cell lung cancer. Biotechnol Genet Eng Rev. 2024;40(4):4205–14. https://doi.org/10.1080/02648725.2023.2208449.
78. Jiang C, Zhao M, Hou S, et al. The indicative value of serum tumor markers for metastasis and stage of non-small cell lung cancer. Cancers (Basel). 2022;14(20):5064. https://doi.org/10.3390/cancers14205064.
79. Zheng Y, Jia R, Li J, Tian X, Qian Y. Curcumin- and resveratrol-co-loaded nanoparticles in synergistic treatment of hepatocellular carcinoma. J Nanobiotechnol. 2022;20(1): 339. https://doi.org/10.1186/s12951-022-01554-y.
80. Li M, Liu T, Cheng W, Jin H, Wang X. A test of miR-128-3p and miR-33a-5p in serum exosome as biomarkers for auxiliary diagnosis of non-small cell lung cancer. J Thorac Dis. 2023;15(5):2616–26. https://doi.org/10.21037/jtd-23-398.
81. Ma Y, Qiu C, Wang B, et al. Autoantibody against tumor-associated antigens as diagnostic biomarkers in hispanic patients with hepatocellular carcinoma. Cells. 2022;11(20):3227. https://doi.org/10.3390/cells11203227.
82. Kaiser AM, Gatto A, Hanson KJ, et al. p53 governs an AT1 differentiation programme in lung cancer suppression. Nature. 2023;619(7971):851–9. https://doi.org/10.1038/s41586-023-06253-8.
83. Gao Y, Zhang N, Zeng Z, et al. LncRNA PCAT1 activates SOX2 and suppresses radioimmune responses via regulating cGAS/STING signalling in non-small cell lung cancer. Clin Transl Med. 2022;12(4): e792. https://doi.org/10.1002/ctm2.792.
84. Mu Y, Li J, Xie F, Xu L, Xu G. Efficacy of autoantibodies combined with tumor markers in the detection of lung cancer. J Clin Lab Anal. 2022;36(8): e24504. https://doi.org/10.1002/jcla.24504.
85. Yang G, Xiao Z, Tang C, Deng Y, Huang H, He Z. Recent advances in biosensor for detection of lung cancer biomarkers. Biosens Bioelectron. 2019;141: 111416. https://doi.org/10.1016/j.bios.2019.111416.
86. Tang ZM, Ling ZG, Wang CM, Wu YB, Kong JL. Serum tumor-associated autoantibodies as diagnostic biomarkers for lung cancer: a systematic review and meta-analysis. PLoS ONE. 2017;12(7): e0182117. https://doi.org/10.1371/journal.pone.0182117.
87. Cai R, Zhao F, Zhou H, et al. A tumor-associated autoantibody panel for the detection of non-small cell lung cancer. Front Oncol. 2022;12:1056572. https://doi.org/10.3389/fonc.2022.1056572.
88. Du Q, Yu R, Wang H, et al. Significance of tumor-associated autoantibodies in the early diagnosis of lung cancer. Clin Respir J. 2018;12(6):2020–8. https://doi.org/10.1111/crj.12769.
89. Ignatiadis M, Sledge GW, Jeffrey SS. Liquid biopsy enters the clinic - implementation issues and future challenges. Nat Rev Clin Oncol. 2021;18(5):297–312. https://doi.org/10.1038/s41571-020-00457-x.
90. Zhong X, Zhang H, Zhu Y, et al. Circulating tumor cells in cancer patients: developments and clinical applications for immunotherapy. Mol Cancer. 2020;19(1):15. https://doi.org/10.1186/s12943-020-1141-9.
91. Andree KC, van Dalum G, Terstappen LW. Challenges in circulating tumor cell detection by the Cell Search system. Mol Oncol. 2016;10(3):395–407. https://doi.org/10.1016/j.molonc.2015.12.002.
92. Lin D, Shen L, Luo M, et al. Circulating tumor cells: biology and clinical significance. Signal Transduct Target Ther. 2021;6(1):404. https://doi.org/10.1038/s41392-021-00817-8.
93. Lawrence R, Watters M, Davies CR, Pantel K, Lu YJ. Circulating tumour cells for early detection of clinically relevant cancer. Nat Rev Clin Oncol. 2023;20(7):487–500. https://doi.org/10.1038/s41571-023-00781-y.
94. Ju S, Chen C, Zhang J, et al. Detection of circulating tumor cells: opportunities and challenges. Biomark Res. 2022;10(1):58. https://doi.org/10.1186/s40364-022-00403-2.
95. Bahmaie N, Ozensoy Guler O, Simsek E. A revolutionary era in advancing precision immuno-oncology; role of circulating tumor cells. J Liquid Biops. 2024;6: 100169. https://doi.org/10.1016/j.jlb.2024.100169.
96. Du C, Tan L, Xiao X, et al. Detection of the DNA methylation of seven genes contribute to the early diagnosis of lung cancer. J Cancer Res Clin Oncol. 2024;150(2):77. https://doi.org/10.1007/s00432-023-05588-z.
97. Mathios D, Johansen JS, Cristiano S, et al. Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nat Commun. 2021;12(1):5060. https://doi.org/10.1038/s41467-021-24994-w.
98. Mattox AK, Douville C, Wang Y, et al. The origin of highly elevated cell-free DNA in healthy individuals and patients with pancreatic, colorectal, lung, or ovarian cancer. Cancer Discov. 2023;13(10):2166–79. https://doi.org/10.1158/2159-8290.Cd-21-1252.

99. Xue R, Li X, Yang L, et al. Evaluation and integration of cell-free DNA signatures for detection of lung cancer. Cancer Lett. 2024;604: 217216. https://doi.org/10.1016/j.canlet.2024.217216.
100. Lin C, Liu X, Zheng B, Ke R, Tzeng CM. Liquid biopsy, ctDNA diagnosis through NGS. Life. 2021;11(9): 890. https://doi.org/10.3390/life11090890.
101. Liang W, Zhao Y, Huang W, et al. Non-invasive diagnosis of early-stage lung cancer using high-throughput targeted DNA methylation sequencing of circulating tumor DNA (ctDNA). Theranostics. 2019;9(7):2056–70. https://doi.org/10.7150/thno.28119.
102. Chabon JJ, Hamilton EG, Kurtz DM, et al. Integrating genomic features for non-invasive early lung cancer detection. Nature. 2020;580(7802):245–51. https://doi.org/10.1038/s41586-020-2140-0.
103. Cristiano S, Leal A, Phallen J, et al. Genome-wide cell-free DNA fragmentation in patients with cancer. Nature. 2019;570(7761):385–9. https://doi.org/10.1038/s41586-019-1272-6.
104. García-Pardo M, Makarem M, Li JJN, Kelly D, Leighl NB. Integrating circulating-free DNA (cfDNA) analysis into clinical practice: opportunities and challenges. Br J Cancer. 2022;127(4):592–602. https://doi.org/10.1038/s41416-022-01776-9.
105. Deb A, Gupta S, Mazumder PB. Exosomes: a new horizon in modern medicine. Life Sci. 2021;264: 118623. https://doi.org/10.1016/j.lfs.2020.118623.
106. Khan NA, Asim M, Biswas KH, et al. Exosome nanovesicles as potential biomarkers and immune checkpoint signaling modulators in lung cancer microenvironment: recent advances and emerging concepts. J Exp Clin Cancer Res. 2023;42(1):221. https://doi.org/10.1186/s13046-023-02753-7.
107. Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem. 2019;88:487–514. https://doi.org/10.1146/annurev-biochem-013118-111902.
108. Mathieu M, Martin-Jaular L, Lavieu G, Théry C. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. Nat Cell Biol. 2019;21(1):9–17. https://doi.org/10.1038/s41556-018-0250-9.
109. Wu J, Li S, Zhang P. Tumor-derived exosomes: immune properties and clinical application in lung cancer. Cancer Drug Resist. 2022;5(1):102–13. https://doi.org/10.20517/cdr.2021.99.
110. Irani K, Siampour H, Allahverdi A, Moshaii A, Naderi-Manesh H. Lung cancer cell-derived exosome detection using electrochemical approach towards early cancer screening. Int J Mol Sci. 2023;24(24): 17225. https://doi.org/10.3390/ijms242417225.
111. Zhang X, Sai B, Wang F, et al. Hypoxic BMSC-derived exosomal miRNAs promote metastasis of lung cancer cells via STAT3-induced EMT. Mol Cancer. 2019;18(1):40. https://doi.org/10.1186/s12943-019-0959-5.
112. Hong H, Lu Y, Zhu X, et al. Cytotoxicity of nitrogenous disinfection byproducts: a combined experimental and computational study. Sci Total Environ. 2023;856(Pt 2): 159273. https://doi.org/10.1016/j.scitotenv.2022.159273.
113. Liu F, Wang Y, Gu H, Wang X. Technologies and applications of single-cell DNA methylation sequencing. Theranostics. 2023;13(8):2439–54. https://doi.org/10.7150/thno.82582.
114. Nishiyama A, Nakanishi M. Navigating the DNA methylation landscape of cancer. Trends Genet. 2021;37(11):1012–27. https://doi.org/10.1016/j.tig.2021.05.002.
115. Pan H, Renaud L, Chaligne R, et al. Discovery of candidate DNA methylation cancer driver genes. Cancer Discov. 2021;11(9):2266–81. https://doi.org/10.1158/2159-8290.Cd-20-1334.
116. Liang W, Chen Z, Li C, et al. Accurate diagnosis of pulmonary nodules using a noninvasive DNA methylation test. J Clin Invest. 2021;131(10): e145973. https://doi.org/10.1172/jci145973.
117. He J, Wang B, Tao J, et al. Accurate classification of pulmonary nodules by a combined model of clinical, imaging, and cell-free DNA methylation biomarkers: a model development and external validation study. Lancet Digit Health. 2023;5(10):e647–56. https://doi.org/10.1016/s2589-7500(23)00125-5.
118. Pan Y, Liu G, Zhou F, Su B, Li Y. DNA methylation profiles in cancer diagnosis and therapeutics. Clin Exp Med. 2018;18(1):1–14. https://doi.org/10.1007/s10238-017-0467-0.
119. Wu R, Zhang B, He M, Kang Y, Zhang G. MicroRNA biomarkers and their use in evaluating the prognosis of lung cancer. J Cancer Res Clin Oncol. 2023;149(18):16753–61. https://doi.org/10.1007/s00432-023-05404-8.
120. Chen Y, Zitello E, Guo R, Deng Y. The function of LncRNAs and their role in the prediction, diagnosis, and prognosis of lung cancer. Clin Transl Med. 2021;11(4): e367. https://doi.org/10.1002/ctm2.367.
121. Bonizzato A, Gaffo E, Te Kronnie G, Bortoluzzi S. Circrnas in hematopoiesis and hematological malignancies. Blood Cancer J. 2016;6(10):e483. https://doi.org/10.1038/bcj.2016.81.
122. Wang R, Xu Y, Tong L, Zhang X, Zhang S. Recent progress of exosomal lncRNA/circRNA-miRNA-mRNA axis in lung cancer: implication for clinical application. Front Mol Biosci. 2024;11:1417306. https://doi.org/10.3389/fmolb.2024.1417306.
123. Suri C, Swarnkar S, Bhaskar L, Verma HK. Non-coding RNA as a biomarker in lung cancer. Non-coding RNA. 2024;10(5):50. https://doi.org/10.3390/ncrna10050050.
124. Wang C, Liu H. Factors influencing degradation kinetics of mRNAs and half-lives of microRNAs, circRNAs, lncRNAs in blood in vitro using quantitative PCR. Sci Rep. 2022;12(1):7259. https://doi.org/10.1038/s41598-022-11339-w.
125. Pei Q, Luo Y, Chen Y, Li J, Xie D, Ye T. Artificial intelligence in clinical applications for lung cancer: diagnosis, treatment and prognosis. Clin Chem Lab Med. 2022;60(12):1974–83. https://doi.org/10.1515/cclm-2022-0291.
126. Huang S, Yang J, Shen N, Xu Q, Zhao Q. Artificial intelligence in lung cancer diagnosis and prognosis: current application and future perspective. Semin Cancer Biol. 2023;89:30–7. https://doi.org/10.1016/j.semcancer.2023.01.006.
127. Hammad M, ElAffendi M, El-Latif AAA, Ateya AA, Ali G, Plawiak P. Explainable AI for lung cancer detection via a custom CNN on CT images. Sci Rep. 2025;15(1):12707. https://doi.org/10.1038/s41598-025-97645-5.
128. Duan X, Ouyang Z, Bao S, et al. Factors associated with overdiagnosis of benign pulmonary nodules as malignancy: a retrospective cohort study. BMC Pulm Med. 2023;23(1):454. https://doi.org/10.1186/s12890-023-02727-7.
129. Snoeckx A, Reyntiens P, Desbuquoit D, et al. Evaluation of the solitary pulmonary nodule: size matters, but do not ignore the power of morphology. Insights Imaging. 2018;9(1):73–86. https://doi.org/10.1007/s13244-017-0581-2.
130. Geppert J, Asgharzadeh A, Brown A, et al. Software using artificial intelligence for nodule and cancer detection in CT lung cancer screening: systematic review of test accuracy studies. Thorax. 2024;79(11):1040–9. https://doi.org/10.1136/thorax-2024-221662.
131. Peters AA, Wiescholek N, Müller M, et al. Impact of artificial intelligence assistance on pulmonary nodule detection and

localization in chest CT: a comparative study among radiologists of varying experience levels. Sci Rep. 2024;14(1):22447. https://doi.org/10.1038/s41598-024-73435-3.
132. Hsu ML, Naidoo J. Principles of immunotherapy in non-small cell lung cancer. Thorac Surg Clin. 2020;30(2):187–98. https://doi.org/10.1016/j.thorsurg.2020.01.009.
133. Robert D, Sathyamurthy S, Singh AK, et al. Effect of artificial intelligence as a second reader on the lung nodule detection and localization accuracy of radiologists and non-radiology physicians in chest radiographs: a multicenter reader study. Acad Radiol. 2024;32(3):1706–17. https://doi.org/10.1016/j.acra.2024.11.003.