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Artificial intelligence-based pharmacological approach in non-small cell lung cancer in the precision medicine era

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ABSTRACT

The increasing knowledge in the molecular pathophysiology of non-small-cell lung cancer (NSCLC) allowed early identification of druggable targets; however, the advanced disease remains incurable mainly due to drug resistance. Therefore, it is essential to explore new methodological approaches for pharmacological strategies based on longitudinal molecular and imaging monitoring of NSCLC evolution, which can support decision-making for personalized treatments in clinical practice and provide new insight for the design of innovative clinical trials. The advent of artificial intelligence (AI) presents an extraordinary opportunity to develop algorithms capable of decoding the complex, multifaceted patterns of NSCLC progression. AI needs input information from biomarker analyses on liquid biopsies, radiomic data, actionable targets involved in cancer drug resistance, and clinically relevant information for choosing personalized next-line therapies, including existing drugs that could target previously unconsidered resistance pathways (drug repurposing), and selecting sequential or combinatorial therapeutic approaches as a fundamental part of precision medicine. This narrative review explores the opportunity of integrating AI-based multiparametric models into reactive and proactive algorithms to offer patients new therapeutic options for long-term quality-adjusted survival.

1. Introduction

The evolution of cancer genomics over the past 20 years has improved our analytical ability to identify oncogenic driver alterations in non-small cell lung cancer (NSCLC). Although the parallel development of innovative drugs has offered patients new opportunities for long-term quality-adjusted survival, advanced NSCLC remains mostly incurable due to a delay in diagnosis and the development of the acquired resistance [1].

Cancer pharmacology and treatment decisions are increasingly based on agnostic criteria [2]. The identification of "druggable" alterations (i.e., predictive biomarkers for which there are approved drugs or standard treatments) and of mechanisms of resistance to treatments could provide the rationale for using targeted drugs strategically, like chess pieces, to steer cancer evolution. The pathway towards this ambitious goal can start with the longitudinal design of pharmacological strategies grounded in molecular and imaging-based monitoring of NSCLC progression, the identification of actionable targets involved in cancer drug

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resistance, and integration of clinically relevant information. This paradigm promises to transform conventional medical services into predictive and personalized frameworks, supported by tools such as next-generation sequencing (NGS) of tumor-derived nucleic acids (i.e., cell-free DNA) in liquid biopsies and radiomic investigations [3,4].

Artificial intelligence (AI) and machine learning (ML) offer powerful modalities of processing large, complex datasets to develop algorithms capable of decoding the intricate patterns of NSCLC progression and identifying sequential or combinatorial therapeutic strategies. These approaches could mitigate treatment delays or failures due to tumor heterogeneity and inter-patient variability in real-world settings (Fig. 1). While current clinical practice typically responds to clinical or radiographic progression, AI-driven models offer the potential to anticipate molecular adaptation before macroscopic relapse. By integrating tumor-derived molecular profiles, radiomic features, and longitudinal clinical metadata, AI may enable proactive intervention strategies that improve survival and quality-adjusted life years. On the other hand, early intervention also introduces risks, potentially exposing patients with only marginal molecular changes to unnecessary toxicity, psychological distress, or financial burden. Treatment modifications must therefore be guided by robust predictive accuracy and validated through prospective clinical studies with relevant endpoints, such as progression-free survival and patient-reported outcomes. Furthermore, concerns about accuracy, transparency, and data security must be addressed, as some individuals may feel uncomfortable with AI-assisted clinical decision-making [5].

This article outlines a perspective of multimodal approaches for predicting tumor evolution, preventing disease progression, and personalizing treatment in NSCLC. Key components of this framework include standard and emerging pharmacological biomarkers, mechanisms of acquired resistance and available therapies, the role of liquid biopsy and next-generation sequencing, and the integration of AI techniques into clinical practice.

2. Current standard of care in NSCLC

Over the past decades, advances in molecular oncology have transformed the therapeutic landscape of NSCLC, shifting treatment decisions from histology-based criteria to biomarker-driven strategies. Current clinical guidelines recommend comprehensive molecular profiling at diagnosis of advanced NSCLC to identify actionable alterations and stratify patients for targeted therapies. Several genomic aberrations now serve as predictive biomarkers for first-line treatment selection, while immune checkpoint inhibitors are guided by PD-L1 expression levels and tumor mutational burden in specific contexts. This section summarizes the molecularly defined subgroups and corresponding therapeutic options that constitute the current standard of care, laying the groundwork for the discussion on resistance mechanisms, liquid biopsy-based monitoring, and AI-enabled decision support in subsequent sections.

2.1. EGFR/ErbB1

Exon 19 in-frame deletions and L858R in exon 21 (85–90 % of all epidermal growth factor receptor (EGFR) mutations) are druggable targets predictive of response to the U.S. Food and Drug Administration (FDA)-approved EGFR tyrosine kinase inhibitors (TKIs), alone or in combination with ramucirumab or bevacizumab (i.e., monoclonal antibodies targeting the extracellular domain of VEGF receptor-type 2). Among the different generations of EGFR TKIs, the National Comprehensive Cancer Network (NCCN) guidelines recommend osimertinib as the preferred first-line treatment for patients with EGFR driver mutations. FDA further recognizes rare EGFR mutations (S768I, L861Q, and G719X) as predictive biomarkers for first line afatinib or osimertinib (Table 1).

NSCLC harboring exon 20 in-frame insertions in the EGFR gene (4 %) are generally unresponsive to EGFR TKIs but can be druggable by amivantamab or mobocertinib (Table 1). Baseline EGFR T790M rarely occurs (0.5 %) and is associated with intrinsic resistance to first- and second-generation EGFR TKIs but is sensitive to osimertinib (Table 1).

2.2. HER2/ErbB2

Somatic HER2/ErbB2 mutations may occur in approximately 3 % of patients with advanced non-squamous NSCLC as a primary event, and most of them (96 %) consist of kinase-activating exon 20 insertions.

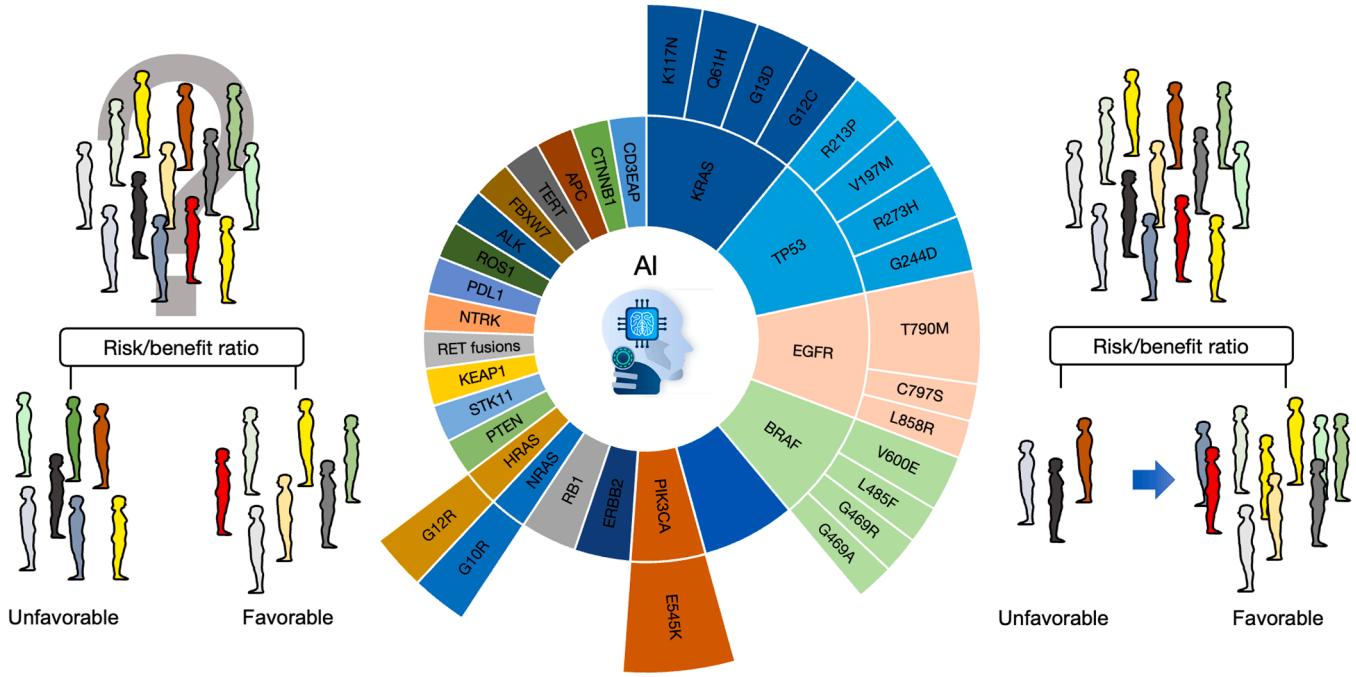

Fig. 1. Improvement in the risk/benefit ratio based on the increasing knowledge of the molecular pathophysiology of non-small-cell lung cancer.

Table 1
Baseline druggable alterations in patients with newly diagnosed advanced NSCLC.

Gene	Druggable targets	Frequency (%)	Drugs		
			Name	Approval status	LoE
ErbB1/EGFR	ex19del, L858R,	85–90	Osimertinib	FDA, EMA	1
	S768I, L861Q, G719X	NA	Afatinib	FDA, EMA	1
	ex20ins	4	Amivantamab, mobocertinib[b]	FDA, EMA	1
	T790M	0.5	Osimertinib	FDA, EMA	1
ErbB2/HER2	Mutation	3	Trastuzumab deruxtecan°[b]	FDA	1
			Trastuzumab Emtansine[b]		2
c-Met	ex14 skipping mutations	3–4	Capmatinib°, tepotinib°	FDA	1
	Gene amplification	1–6	Crizotinib, capmatinib, tepotinib		2
Alk	Rearrangement (fusion)	3–5	Crizotinib, alectinib°, brigatinib°, lorlatinib°	FDA	1
Ros1	Rearrangement (fusion)	1–2	Entrectinib°, crizotinib°	FDA	1
			Ceritinib		2
Ret	Rearrangement (fusion)	1–2	Selpercatinib, pralsetinib°	FDA	1
Braf	Mutations (V600E)	3–8	Dabrafenib plus trametinib°	FDA	1
Kras	Mutations (G12C)		Sotorasib°[b], adagrasib[b]	FDA	1
Ntrk 1//2/3[a]	Gene fusion		Larotrectinib, entrectinib°	FDA	1
TMB*	High		Pembrolizumab	FDA	1

Level 1: FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication. Source: NCCN Guidelines (Version 6.2022 — December 2, 2022); OncoKB (https://www.oncokb.org). LoE: Level of evidence by OncoKB (https://www.oncokb.org). TMB: Tumor Mutational Burden. NA: not available.
[a] All solid tumors. Preferred therapy.
[b] As subsequent treatment after systemic therapy.

ErbB2 exon 20 mutation is a recognized biomarker predictive of response to the antibody-drug conjugates, trastuzumab deruxtecan and trastuzumab emtansine (Table 1). NCCN guidelines recommend trastuzumab deruxtecan as the preferred first-line treatment for this indication [6] (Table 1).

2.3. MET

The mutations leading to exon 14 skipping in the gene encoding for mesenchymal-epithelial transition factor (c-Met) occur with an approximately 3–5 % frequency in NSCLC [7–9]. These mutations result in a juxta-membrane domain lacking MET protein (METΔ14) with an extended half-life after HGF stimulation that has been considered an oncogenic driver event [10].

MET TKIs can be classified into three categories: type I, further subdivided into non-selective (crizotinib) and selective (capmatinib, tepotinib, savolitinib) ATP-competitive inhibitors, type II (cabozantinib, merestinib, foretinib, and glesatinib) that are ATP-competitive inhibitors binding to the inactive form of MET, and type III (tivantinib) that bind allosterically outside of the ATP domain [9]. Furthermore, amivantamab is a bispecific antibody targeting EGFR and MET.

METΔ14 predicts response to tepotinib and capmatinib (Table 1). MET amplification (frequency of 2 %) is another major event leading to MET receptor activation that may occur in therapy-naïve NSCLC as a primary event or even the background of EGFR and KRAS mutations, although these co-alterations are rare (0.4–0.6 %) [11,10]. NSCLCs harboring DNA amplification in the c-Met are dependent on MET for growth and survival, while patients with de novo high-level amplification are responsive to crizotinib.

2.4. ALK

Oncogenic ALK gene rearrangements with multiple fusion partners occur in about 5 % of NSCLC patients. The consequent overexpression and ligand-independent activation of ALK make tumors resistant to EGFR TKIs. Testing for ALK rearrangements in patients with advanced NSCLC is based on data showing the efficacy of targeting drugs and on the FDA approvals. Currently approved ALK TKIs for advanced ALK-positive NSCLC were classified into three generations. Next-generation ALK inhibitors including alectinib, brigatinib, and lorlatinib have superior efficacy and better CNS activity compared to crizotinib and are the preferred first-line monotherapy options for patients with ALK-positive metastatic NSCLC (Table 1) [12].

2.5. ROS1

ROS1 gene rearrangements with several partners (the most common is CD74) occur in 1–2 % of NSCLC patients and promote constitutive activation of ROS1 kinase activity. Crizotinib, entrectinib, and ceritinib are recommended as first-line drugs by NCCN. The FDA recognized ROS1 gene rearrangements as biomarkers predictive of response to FDA-approved drugs for this indication, respectively crizotinib, entrectinib, and ceritinib (Table 1). Due to a structure homology, rearrangements of ROS1 and ALK may overlap.

2.6. RET

Fusions of RET emerge from chromosomal translocations and were found in multiple cancers including 1–2 % of NSCLC [13]. The subsequent fusion proteins result in constitutive activation of RET kinase activity that may predict response to the multikinase and RET inhibitors, selpercatinib, and pralsetinib (Table 1) [14,15].

2.7. RAS

Activating KRAS mutations occur in 20–30 % of NSCLC. The most common KRAS mutation, G12C, is a biomarker predictive of response to covalent inhibitors, such as sotorasib and adagrasib. NCCN guidelines recommend sotorasib as the first-line treatment for this indication (Table 1) [16,17].

2.8. BRAF

Somatic mutations in the BRAF gene occur in 3–8 % of lung adenocarcinoma. V600E is the most common (50 %), while G469A/V and D594G may occur in 35 % and 4 % of NSCLC, respectively. The BRAF inhibitors dabrafenib and vemurafenib have clinical activity as a monotherapy; however, BRAF V600E is an FDA-recognized biomarker of response to the combination of dabrafenib and trametinib (a MEK inhibitor) and is recommended as the first-line treatment in BRAF V600E positive NSCLC (Table 1).

2.9. NTRK 1/2/3

The neurotrophic tropomyosin-related kinases (NTRK) gene fusions are found in around 0.2 % of NSCLC, and the NTRK inhibitors, entrectinib, and larotrectinib, were approved in the USA and Europe as either front-line or subsequent treatment options in this specific population (Table 1) [18].

3. Mechanisms of acquired resistance and treatments

Despite recent advances in targeted therapy, therapeutic resistance and disease progression remain major challenges in the treatment of NSCLC, particularly in later lines of therapy. Increasing evidence has identified two main types of resistance mechanisms that cancer cells usually acquire as a counter-response to anticancer drugs. On-target resistance consists of specific alterations in the primary target that make it unresponsive to initially effective therapies. In contrast, off-target resistance arises from the activation of parallel or downstream oncogenic pathways that allow tumors to bypass the inhibited target and sustain malignant growth [19].

3.1. On-target resistance

3.1.1. EGFR

T790M is a somatic mutation in the EGFR gene that produces biochemical changes in the EGFR such that the constitutively activated receptor returns to have an affinity for ATP similar to that of wild-type EGFR. Such a mutation, which was found in approximately 50 % of T790M-positive patients who previously responded to 1st- or 2nd-generation EGFR-TKIs, is a molecular biomarker of acquired resistance to these drugs that is sensitive to osimertinib [20,21]. Recurrent EGFR amplification or loss of EGFR T790M are resistance mechanisms to 3rd-generation EGFR TKIs [22,23].

Compound mutations are two or more mutations present in the same molecule. Osimertinib progression may occur in about one-third of NSCLC patients and is usually associated with tertiary EGFR mutations (C797X, V769M, and V843I) [24,23]. Triple mutation in the EGFR gene (activating EGFR mutations/T790M/C797S) can be resistant to all the available EGFR TKIs. Compelling clinical evidence supports C797S as a biomarker predictive of resistance to osimertinib, and amivantamab seems to have some effects in patients harboring triple EGFR mutations (R2; Table 2) [25]. Acquired resistance mechanisms were identified in tissue and liquid biopsies from advanced EGFR-mutated NSCLC patients treated with osimertinib in first- or in second-line, with MET amplification, EGFR C797S, and SCLC transformation (10 %) the most frequently identified [26]. Interestingly, NGS evaluation of SCLC-transformed biopsies showed that osimertinib administered as a second-line treatment was able to eliminate the EGFR-T790M cell population while consolidating the proliferation of the TP53 + RB1 clone which ultimately led to the histologic transformation to SCLC [27].

3.1.2. ALK

The molecular profiling of ALK mutations in ALK-resistant NSCLC may differ based on prior targeted drugs (Table 2). G1202R/del is the most common on-target resistance mechanism found in >50 % of NSCLC in patients previously exposed to 2nd generation ALK TKIs, while other resistance mutations were found to be specific ceritinib or alectinib resistance mechanisms (Table 2) [28]. Of note, lorlatinib is effective on all the most common single ALK mutations found in ALK-resistant NSCLC patients, including G1202R/del [29,28].

Multiple ALK mutations acquired during treatment with different ALK TKI generations are therapeutically challenging. For example, subsequent treatments after progression with the same first-line ALK TKI may also generate compound mutations found to be resistant to all the approved ALK-TKIs [29,30]. Of note, some compound mutations resistant to lorlatinib (I1171N/L1256F and C1156Y/L1198F) may result in re-sensitization to 1st or 2nd generation ALK TKIs [31] (Table 2).

3.1.3. MET

On-target resistance, including kinase domain mutations in codons H1094, G1163, L1195, D1228, and Y1230, and amplification of the MET exon 14-mutant allele, were observed in a third of patients treated with MET TKIs. Second site mutations in the MET activation loop (MET D1228N and Y1230C) in MET ex14 mutated NSCLC are resistance mechanisms to type I MET TKIs (e.g., crizotinib) that retain sensitivity to type II MET TKIs (e.g., cabozantinib) [32].

3.1.4. RET

RET mutations at the solvent front and the hinge may occur at a relatively low frequency in patients with RET fusion-positive NSCLC. These mutations were found to be important resistance mechanisms for both selpercatinib and pralsetinib (Table 2) [14]. Furthermore, gatekeeper mutations affecting the V804 residue have been reported in the selpercatinib-resistant case [33,34] (Table 2).

Table 2
On-target resistance mechanisms and treatments.

Target	Biomarker	Frequency (%)	Victim drug	Treatment	
				Approved/ preferred	Investigational
EGFR	T790M	50	1st and 2nd gen TKIs	Osimertinib	
	EGFR amplification or loss of EGFR T790M	NA	All EGFR TKIs		
	Compound mutations (C797X, V769M, and V843I)	NA	All EGFR TKIs	None	Amivantamab
ALK	G1202R	50	1st and 2nd gen ALK TKIs	Lorlatinib	
	G1269A, F1174X, L1196M, I1171T, and D1203N	10	Crizotinib	Lorlatinib	
	G1128A, G1269A, I1171T/E1210K		Ceritinib	Lorlatinib*	
	W1295C, G1202R/L1196M		Alectinib	Lorlatinib*	
	I1171N/L1256F, and C1156Y/L1198F		Lorlatinib	None	1st and 2nd gen ALK TKIs
	G1202R/G1269A		Lorlatinib	None	
	I1171N/F1174I and I1171N/L1198H		All ALK TKIs		
ROS1	G2032R				
MET	H1094, G1163, L1195, D1228, Y1230, and MET amplification	30–35	All MET TKIs	None	
	MET ex14 mutated	NA	Type I MET TKIs (crizotinib)	None	Type II MET TKIs (cabozantinib)
RET	V738A, G810C/S/R, Y806C/N	NA	Selpercatinib, pralsetinib		

NA: not available.

3.2. Off-target resistance

3.2.1. EGFR

MET amplification is a common mechanism for bypassing EGFR inhibition (10–25 %) found in NSCLC patients progressing on EGFR TKIs, particularly those treated with osimertinib. Although no therapies are currently available in this patient population, this alteration may predict response to tepotinib and capmatinib, albeit on a lower level of evidence than NSCLC with MET exon 14 skipping mutations (Table 3). Furthermore, these patients may benefit from combined treatment with osimertinib and the MET inhibitor, savolitinib [35].

ErbB2 amplification is another common bypass mechanism in EGFR-mutated NSCLC (10–15 %) after 1st- or 2nd-generation EGFR TKIs and may also occur after osimertinib progression [24,36]. Although no currently HER2-specific targeted therapies have been approved for patients with EGFR-mutant NSCLC who develop resistance via ErbB2 amplification, several potentially effective HER2 targeting drugs include moAbs, antibody-drug conjugates (ADCs), and TKIs (Table 3). The NCCN guidelines indicated trastuzumab deruxtecan as a preferred subsequent therapy option for patients with ErbB2 mutation-positive metastatic NSCLC who progress on EGFR TKI therapy.

KRASG12C mutation, which was detected in T790M negative patients (~1 %) after the development of EGFR-TKI resistance [37], is druggable with the irreversible inhibitor sotorasib [38].

Resistance to early-generation EGFR TKIs was also found after the acquisition of BRAF mutations (G469A or V600E), whereas NRAS o KRAS copy number gain can occur as a resistance mechanism to osimertinib [24,39].

PI3KCA mutation, loss of PTEN, and increased mTOR expression may induce resistance to EGFR TKIs. JAK-STAT pathway seems to be an early adaptative counter-response to EGFR TKI treatments. Noteworthy, EGFR can harbor multiple oncogenic (e.g., recurrent amplification), which might contribute to osimertinib resistance, while other alterations in osimertinib-associated resistant genes (EGFR C797X, MET, BRAF, PIK3CA, KRAS, NRAS, MAP2K1) are generally mutually exclusive with each other [24].

3.2.2. ALK/ROS1

Several patients with ALK- or ROS1-rearranged tumors treated with crizotinib showed increased EGFR activation as a bypass resistance mechanism [40]. Other ALK-independent resistance mechanisms that can make NSCLC cells refractory to further ALK inhibition are reported in Table 3. Mechanisms of resistance to novel generation ALK TKIs may be caused by selective genetic pressure. NF2 loss-of-function mutations were described as a mechanism associated with the lorlatinib resistance [31]. Furthermore, activating MEK1 mutations were found to be associated with resistance to ALK TKIs, whereas KRAS or NRAS mutations were associated with crizotinib resistance in ROS1-rearranged NSCLC cells. PI3K-AKT pathway did not seem to be involved as a resistance mechanism in ALK- or ROS1-rearranged NSCLC cells [29]. Owing to the structural analogy between the two TK domains, several ROS1 mutations (e.g., S1986Y/F) are analogous to ALK mutations (e.g., C1156Y) and confer resistance to the same drug (e.g., crizotinib).

3.2.3. MET

Off-target resistance to MET TKIs detected in NSCLC patients primarily includes single or compound amplifications in various genes with no therapeutic options to overcome resistance (Table 3) [32].

3.2.4. RET

MET amplification is the major off-target mechanism of resistance to RET inhibitors [14]. MET activation was found as a targetable mediator of resistance to RET-directed therapy, and combined selpercatinib with the multikinase inhibitor, crizotinib, appears to be a promising therapeutic option (Table 3) [15].

3.2.5. KRAS

A heterogeneous resistance genetic signature was found in approximately 60 % of patients with KRAS G12C-positive NSCLC treated with sotorasib (Table 3). Other events included the amplification of EGFR, FGFR2, MET, and MYC [41].

4. Emerging biomarkers in NSCLC

In addition to well-established driver mutations, several emerging biomarkers are being investigated to refine patient stratification and guide treatment decisions in NSCLC. These include tumor mutational burden (TMB) and microsatellite instability (MSI), which may predict response to immunotherapy, as well as radiomic features extracted from imaging data that may reflect tumor heterogeneity, immune infiltration, or microenvironmental dynamics. While not yet fully standardized for clinical use, these biomarkers are being incorporated into research protocols and early clinical workflows. This section summarizes their current status, predictive potential, and limitations (Tables 4, 5).

Table 3
Off-target resistance mechanisms and treatments.

Target	Biomarker	Frequency (%)	Victim drug	Treatment	
				Approved/preferred	Investigational
EGFR	MET amplification	5–30	Osimertinib, 1st gen EGFR TKIs	Capmatinib, tepotinib	Osimertinib plus savolitinib
	ErbB2 amplification	12	1st gen EGFR TKIs	Trastuzumab deruxtecan	TDM-1, pertuzumab, trastuzumab, HER2 TKIs
		2–5	Osimertinib	None	None
	ALK rearrangements	3	Osimertinib, 1st gen EGFR TKIs		
	KRASG12C mutation*	1	EGFR TKIs	Sotorasib	Not available
	BRAF mutations (G469A and V600E) and rearrangements	2.5–5	All EGFR TKIs		
	NRAS or KRAS copy number gain or mutations*	2–7	Osimertinib		Not available
	PI3KCA mutation, loss of PTEN*	4	Osimertinib		Not available
	NTRK rearrangements	1–2	Osimertinib		None
	FGFR3 rearrangements	1–2.5	Osimertinib		
ALK	MET amplification and rearrangements	15–25	2nd and 3rd gen ALK TKIs		Not available
	EGFR activation and mutations	53–58	Crizotinib		Not available
	IGF1R activation	80	Crizotinib		Not available
	KRAS mutations	18	Crizotinib		Not available
	NF2 mutations	20	Lorlatinib		Not available
MET	Amplification of various genes	?	All MET TKIs	None	None
RET	MET amplification	15	All RET TKIs		Selpercatinib plus crizotinib

Table 4
NGS-based application in NSCLC.

Drug	Type of biopsy	Cut-off value (mut/Mb)	Aim	NGS platform	Clinical outcome	References
Atezolizumab	Liquid	≥16	Prediction of response	FoundationOne Liquid Companion Diagnostic assay (CDx)	ORR	[42]
Atezolizumab	Liquid	≥16	Prediction of response	FoundationOne Liquid Companion Diagnostic assay (CDx)	Improved clinical benefit vs. chemotherapy in non-squamous NSCLC	[43]
Atezolizumab		≥16		Designed panel	Improved PFS vs. docetaxel	[42]
Durvalumab plus Tremelimumab		≥ 20	Prediction of response	GuardantOMNI assay	Improved OS vs. chemotherapy	[44]
Osimertinib	Tissue, liquid		Identify druggable targets of resistance	Homemade Bypass Genes Mutation Panel, Ion AmpliSeqTM Library Kit 2.0, and Ion XpressTM Barcode Adapters Kit	Not reported	[29]
ALK inhibitors	Liquid	None	Identify druggable targets of resistance	Oncomine™ Pan-Cancer Cell-Free Assay kit	Not reported	[45]

ORR: overall response rate; PFS: progression-free survival; OS: overall survival.

4.1. Tumor mutational burden

The analysis of tumor mutational burden (TMB), expressed as the number of mutations per megabase (mut/Mb), is usually carried out on tissue biopsies; however, the quantity of tumor specimens could not be optimal with turnaround times of weeks from sample receipt to test result [70]. Liquid biopsies using circulating tumor DNA isolated from blood may exceed these limitations and are already available for real-world testing (Table 4). Blood TMB correlates with tumor TMB [71], and targeted NGS panels are faster and less expensive than whole-exome sequencing [71].

The role of TMB as a reliable biomarker that predicts response to immune checkpoint inhibitors (ICIs) was demonstrated first in patients with NSCLC or melanoma, where those having higher levels of TMB experienced improved outcomes. Since then, TMB has emerged as a powerful predictor across different cancer types, and recommendations from the NCCN strongly advise the determination of TMB as an emerging biomarker for patient candidates for ICI [72]. In line with this, a high TMB in ctDNA of NSCLC patients treated with atezolizumab predicted a longer overall survival (OS) than the low subgroups [42]. Specifically, TMB was higher in patients treated with ICIs who experienced durable clinical benefit versus those who did not (8.5 vs. 6.6 mutations/Mb). Finally, the median TMB value appeared to be predictive rather than prognostic since no correlation was observed in patients not treated with ICIs [73].

4.2. Microsatellite instability

Mismatch repair (MMR) is a fundamental mechanism in repairing DNA damage that usually occurs in microsatellites. Deficient MMR (dMMR) can make cells unable to repair damaged DNA, thus leading to the accumulation of mutations with high microsatellite instability (MSI-H). It is worth mentioning that mechanisms other than MSI-H can drive tumors to acquire more mutations [74]. The prevalence of MSI-H in lung adenocarcinoma is similar to that of other alterations (approximately 1–5 %) [75], and tumors harboring EGFR, KRAS, or BRAF mutations show high proliferation rates [76]. Of note, it has been recognized that patients with NSCLC characterized by MSI-H may benefit from ICI [77, 75].

4.3. Radiomics features

Compelling evidence shows PET image-based radiomics as a powerful tool to evaluate the spatiotemporal tumor heterogeneity in lung cancer patients, especially when tissue samples are not available [78]. Radiomic has been used to identify features that predict EGFR-TKI response based on metastasis/brain parenchyma interface [79]. Several studies in advanced NSCLC patients were carried out combining radiomics, laboratory results, and clinicopathological data to build machine-learning models able to predict response to anti-PD-1/PD-L1 agents [80–82]. However, translating radiomic features into clinical decision-making is difficult due to multiple steps (e.g., manual segmentation of tumor boundaries, feature extraction, and selection) [54].

5. Tissue vs liquid biopsies for molecular profiling

Tissue biopsy remains the gold standard for molecular profiling in NSCLC, providing histological confirmation and comprehensive genomic analysis. However, its use is often limited by procedural invasiveness, insufficient sample quantity, and the challenge of capturing tumor spatial heterogeneity. Liquid biopsy offers a minimally invasive and repeatable alternative for the detection and monitoring of tumor-derived molecular alterations, enabling dynamic assessment of tumor evolution and heterogeneity in real time [71]. Among the different circulating analytes under investigation – including circulating tumor cells (CTCs), extracellular vesicles (EVs), RNA, and non-coding miRNA analytes – circulating free DNA (cfDNA) and circulating tumor DNA (ctDNA) have garnered significant attention for their utility in cancer patients [83–86]. The process of liquid biopsy analysis and the detection of mutations through NGS technology is reported in Fig. 1.

This section compares tissue and liquid biopsy in terms of their analytical performance, clinical utility, and ability to guide treatment decisions. Focus is given to the detection of actionable alterations, the measurement of tumor mutational burden (TMB), and the role of each approach in managing resistance and informing longitudinal treatment adaptation.

5.1. Analytical performance and concordance

Numerous studies have demonstrated that NGS-based analysis of ctDNA provides a reliable alternative to tissue genotyping in NSCLC. Reported sensitivities range from 75 % to 90 %, with high concordance rates especially for EGFR activating mutations, P53, RB1, KRAS (G12C), PIK3CA, MET, CD3EAP, CTNNB1, ERBB2, APC, BRAF, TERT, FBXW7, and HRAS detection [87–95]. The ability to detect these alterations makes the tumor suitable for targeted therapies and can significantly impact clinical outcomes [96–100].

In some cases, ctDNA testing may even outperform tissue-based assays. For example, a study conducted by Wang and colleagues demonstrated a better specificity of ctDNA in the detection of EGFR mutations in NSCLC patients compared to tissue biopsy [100]. A specificity of 0.98 (95 % CI = 95–99 %) and a sensitivity of 0.68 (95 % CI = 60–75 %) was calculated for cfDNA. In another study conducted in NSCLC patients, the analysis of ctDNA found additional T790M point mutations in 3 patients

Table 5
AI-based strategies in NSCLC.

Modality	Data	ML Model	Aim	Reference
Unimodal	WSI	CNN (inception v3)	Diagnosis of lung cancer, prediction of mutational status	[46]
	CT images	Random Forest	OS prediction	[47]
	Digitalized PD-L1 IHC-stained slides	AC-GAN	Scoring of PD-L1 expression in late-stage NSCLC needle biopsies	[48]
	Radiomic features	LASSO	Histology subtype classification	[49]
	Radiomic features	Random Forest	Predict cell proliferation	[50]
	CT images	CNN	Predict EGFR mutation status	[51]
	CT images	Random Forest	Predict treatment sensitivity	[52]
	CT images	3D Densely Connected CNN	Distinguish high-TMB from low-TMB patients with advanced NSCLC	[4]
	PET/CT images	SResCNN	Predict EGFR mutation status	[53]
	CT images	Bidirectional GAN	Predict EGFR-TKI efficacy in advanced EGFR–positive NSCLC	[54]
	WSI	CLAM	NSCLC subtyping	[55]
	Gene expression	DNN	Predict response to ICI	[56]
	WSI	DNN	PFS prediction in advanced NSCLC patients treated with ICI	[57]
	CT images	Densely Connected CNN	Prediction of EGFR genotype and PFS of NSCLC patients treated with EGFR-TKI	[58]
	Clinical data	XGBoost	Predict prognosis (OS, DFS, CSS)	[59]
	Gene mutation	DNN	OS prediction	[60]
	Radiomic features	XGBoost, SVM, RF, LR, KNN, DT, AdaBoost	Prediction of PD-L1 and PFS	[61]
	WSI	CNN (ResNet-18)	Predict brain metastasis	[62]
Multimodal	Gene expression, clinical data	DNN	OS prediction	[63]
	Gene expression, radiomics	Logic learning machine	Predict histotype and tumor recurrence	[64]
	Genomics, transcriptomics, clinical	XGBoost	Predict response to ICI	[65]
	Radiomics, clinical	Logistic regression	Predict tumor immune profiles	[66]
	CT images, digitalized PD-L1 IHC-stained slides, genomic features	DyAM	Predict response to PD-L1 blockade in patients with advanced NSCLC	[67]
	Radiomics, deep features, clinical, transcriptomics	Deep learning and classical machine learning models	Predict OS and therapy response	[68]
	CT images, clinical	CNN	Predict EGFR mutations	[69]

AC-GAN: Auxiliary Classifier Generative Adversarial Network; AdaBoost: Adaptive Boosting; CLAM: Clustering-constrained-attention multiple-instance learning; CSS: Cancer-specific survival; CNN: Convolutional Neural Network; DNN: Deep Neural Network; DSF: Disease-free survival; DT: Decision Tree; DyAM: Dynamic deep attention-based multiple-instance learning model with masking; EGFR: Epidermal growth factor receptor; ICI: Immune Checkpoint Inhibitors; KNN: K-nearest neighborhood; XGBoost: eXtreme Gradient Boosting; LASSO: least absolute shrinkage and selection operator; LG: Logistic Regression; NSCLC: Non-Small Cell Lung Cancer; OS: Overall Survival; PFS: Progression Free Survival; RF: Random Forest; SResCNN: 2D small-residual-convolutional-network; SVM: Support Vector Machines; TMB: Tumor Mutational Burden; WSI: Whole-Slide Images.

that were not detected in the tissue [101]. Similarly, Buburuzan and colleagues demonstrated that EGFR L858R (19.23 %), KRAS G13D and Q61H (15.38 %), and TP53 G244D, V197M, R213P, and R273H (50 %) alterations were detectable exclusively in ctDNA, but not in matched tissue samples [102].

5.2. Clinical guidelines

Major international guidelines now support the use of plasma testing at diagnosis when tissue DNA is insufficient or no mutation can be detected [87]. The National Comprehensive Cancer Network (NCCN), the European Medicines Agency (EMA), and the College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP) issued recommendations advocating for repeat biopsy and/or plasma testing to identify clinically relevant alterations when tissue sampling is insufficient or difficult to analyze [103,104]. Furthermore, the European Society for Medical Oncology (ESMO), recommended the use of liquid biopsy testing to detect oncogenic alterations in EGFR, BRAF, ALK, ROS1, PD-L1 expression, and NTRK genes, in diagnosed advanced lung adenocarcinoma patients [105].

5.3. Resistance detection and longitudinal monitoring

Liquid biopsy enables real-time tracking of acquired resistance. ctDNA profiling has rapidly evolved from single-gene assays to comprehensive genome profiling (CGP) using NGS [106,107], an approach found to be particularly useful at the biomarker switch (i.e., when there is a change in ctDNA biomarkers during therapy including the acquisition of resistance-related mutations) [106]. For instance, RB1 mutations and TP53 loss have been identified as potential biomarkers associated with decreased efficacy of TKIs and high risk of small cell transformation for patients with NSCLC [108,109]. It is worth mentioning that patients with EGFR mutation/RB1 alterations/TP53 loss are at high risk of small cell lung cancer transformation; otherwise, predictive role of RB1 mutations and TP53 loss may not apply to patients with EGFR WT NSCLC.

NGS has also proven superior to other platforms, such as d-PCR and RT-PCR, in the detection of acquired T790M mutation in plasma [110]. In a study conducted by Dono and colleagues [111], a tag-based NGS panel detected both EGFR activating mutations and T790M more frequently than RT-PCR in the plasma of 42 NSCLC patients. Similarly,

the analysis of ctDNA from 77 patients treated with rociletinib, detected alterations including amplifications and fusions responsible for treatment resistance such as KRAS Q61H and K117N, HRAS G12R, and NRAS G10R, EGFR C797S, PIK3CA E545K point mutations, and MET amplification in 19 % of cases [112]. In addition to the well-known resistance mechanisms such as MET amplification, ERBB2 amplification, and single nucleotide variants (SNVs) of PIK3CA and BRAF V600E, rarer variants of BRAF G469A/G469R and L485F were also detected using ctDNA analysis through NGS [113]. Moreover, in a study involving 210 NSCLC patients, ctDNA analysis revealed secondary resistance mechanisms that directly informed treatment decisions [114]. More specifically, patients acquiring EGFR T790M mutation were subsequently treated with osimertinib targeted therapies, whereas patients who acquired MET amplification were subsequently treated with osimertinib in combination with a MET inhibitor. Furthermore, patients with the pV600E variant of BRAF were treated with dabrafenib and trametinib, patients exhibiting MET exon 14 skipping were treated with crizotinib, and in one patient, where RET fusion was detected, cabozantinib was used.

The ability to longitudinally monitor clonal evolution positions ctDNA as a key tool for proactive treatment adaptation.

5.4. Plasma tumor mutational burden as a biomarker for immunotherapy

Plasma tumor mutational burden (pTMB) has emerged as a non-invasive predictive biomarker for response to immune checkpoint inhibitors in NSCLC. An FDA-approved NGS platform that analyzes over 300 genes in plasma (Foundation One Liquid CDx, Foundation Medicine) was tested and validated in a metanalysis of randomized trials showing high pTMB ($\geq$16 mut/Mb) associated with response rate and PFS in NSCLC treated with atezolizumab [115,116]. Furthermore, an exploratory analysis using the GuardantOMNI™ assay suggested that pTMB $\geq$ 20 mut/Mb was related to better OS in patients treated with durvalumab and tremelimumab compared to chemotherapy [44]. Baseline pTMB was also found to predict response to pembrolizumab-based therapy in metastatic NSCLC. In particular, OS for patients with pTMB $\geq$ 16 mut/Mb was not reached versus 8.8 months for those with pTMB $<$ 16 mut/Mb. Furthermore, mutations in ERBB2 exon 20, STK11, KEAP1, or PTEN were commonly found in non-responders (i.e., patients with no durable clinical benefit), indicating potential mechanisms of resistance [117].

Despite its promise, the lack of standardized cut-off thresholds, assay variability across sequencing platforms, and influence of ctDNA abundance on mutation detection remain challenges to broad clinical adoption [109]. Addressing these limitations will be essential to ensure reproducibility and clinical utility of pTMB in guiding immunotherapy decisions.

5.5. Limitations and considerations

Despite its significant potential, liquid biopsy has limitations that must be considered for clinical adoption. Recent studies have demonstrated that ctDNA detectability is influenced by various clinical and biological factors. For example, in a large cohort study of lung cancer patients using an in-house 1021-gene panel, ctDNA was more readily detected in treatment-naïve patients, in those with small-cell lung cancer (SCLC), and in NSCLC adenocarcinoma subtypes compared to squamous cell carcinoma [109]. Furthermore, results from a large clinical trial in metastatic NSCLC showed that therapeutically targetable mutation detection (i.e., EGFR, ALK, and BRAF, MET, EGFR T790M, and ALK) was the highest for patients with liver metastases and the lowest for those with M1a disease. These findings suggest that in certain clinical contexts, such as low-burden disease or when ctDNA shedding is minimal, tissue biopsy should be preferred over plasma NGS [87].

Taken together, the integration of liquid biopsy into routine clinical workflows offers a promising complement to tissue-based diagnostics in NSCLC, particularly for treatment selection, resistance monitoring, and immunotherapy stratification. However, careful consideration of technical and biological limitations remains essential for its optimal use.

6. Artificial intelligence in NSCLC

The growing public availability of high-dimensional datasets in the health domain paved the way for the utilization of advanced analytical methodologies, particularly AI techniques (Table 5). In cancer treatment, AI holds promise in selecting therapeutic strategies to enhance drug response, presenting a significant opportunity for improving patient outcomes [118].

6.1. Unimodal AI

Unimodal learning, where a single modality of data (e.g., images) is used for model training, has been successfully applied in recent years to predict treatment response in lung cancer patients. This learning approach has yielded notable advancements, such as the proposal of a bidirectional generative adversarial network (GAN) to predict EGFR-TKI efficacy from computed tomography (CT) images in patients with advanced EGFR–positive NSCLC. The study demonstrated that stratifying patients into the high or low-progression-risk groups based on deep learning semantic signatures led to superior results when compared to previous radiomics methods [54]. Additionally, researchers utilized a semantic segmentation model based on deep neural network (DNN) architecture to investigate the spatial distribution of tumor-infiltrating lymphocytes (TIL) in the tumor microenvironment using whole-slide images. Their findings highlighted the correlation between AI-powered spatial analysis of TIL and tumor response, as well as PFS in advanced NSCLC patients treated with ICIs [57]. Furthermore, DeepGeneX, a computational framework based on DNN, was proposed to predict response to ICIs from gene expression data. The model, initially trained with melanoma patients, identified a clinically actionable biomarker gene set consisting of six genes, successfully validated in other cancer types, including lung [56]. Finally, an interesting example of a fully automated AI system (FAIS) has been recently reported, where deep learning models were trained to predict EGFR genotype from whole-lung information. The system automatically imported original chest CT images of a patient receiving an EGFR-TKI and directly predicted the risk of disease progression. Of note, FAIS can learn to identify patients with an EGFR mutation at high risk of developing drug resistance. This work also suggests that morphological and functional changes in non-tumor tissues of the lungs, such as vascularity in the tumor microenvironment, pleural retraction, and invasion, were associated with the EGFR genotype [58].

While unimodal learning has shown promising results, leveraging multiple data sources and input modalities seems key to improving model predictions and mimicking the multimodal nature of clinical expert decision-making.

6.2. Multimodal AI

Multimodal AI learning has gained increasing interest in healthcare, particularly in neurology and oncology. The integration of multiple data sources, including multi-omics (e.g., genomics, transcriptomics, proteomics), imaging (e.g., CT scans), text (e.g., clinical notes), and clinical data (e.g., patient demographics), aims to complement and augment the information content beyond that of any individual modality, thus mirroring the comprehensive approach inherent in current clinical practice.

In lung cancer, multimodal AI is showing promising results. A dynamic deep attention-based multiple-instance learning model with masking (DyAM) was recently proposed to predict immunotherapy response from a combination of CT images, digitalized PD-L1 IHC-stained slides and genomic features in NSCLC patients [67]. The study showed that the developed model outperformed unimodal measures, including tumor mutational burden and PD-L1 immunohistochemistry

score. Additionally, researchers used deep learning to extract features from CT images, and then integrated them with traditional radiomics, transcriptomics, and clinical data using machine learning models to evaluate NSCLC patient's survival and response to adjuvant chemotherapy [68]. In both cases, the multimodal approach showed improved accuracy when compared with the single-source models. Furthermore, a logic learning machine – an efficient implementation of Switching Neural Networks (SNNs) – was used to predict histotype and tumor recurrence integrating gene expression and radiomic data [64].

The successful integration of multiple data modalities represents a significant advancement in oncology research, particularly in the context of NSCLC, offering promising avenues for personalized treatment strategies. However, to translate these findings into clinical practice, further development of robust and generalizable models is essential.

6.3. Data fusion strategies

While single-modality profiling provides valuable insight into tumor biology, it is often insufficient to capture the full complexity of cancer. Multimodal approaches, which integrate data from different sources, offer a more comprehensive view by leveraging the complementary strengths of each modality. The process of combining these data types is known as data fusion, and it is typically categorized into three strategies: early fusion, intermediate fusion, and late fusion [119].

Early fusion is the most straightforward approach, in which features from multiple data types are concatenated into a single joint feature matrix prior modeling. This strategy allows the simultaneous analysis of all modalities but requires that each sample has complete data across all input types, which can be a limiting factor in clinical settings.

Late fusion involves developing separate unimodal models for each data type and then combining their outputs in a final integrative model. This approach provides flexibility in selecting the most appropriate modelling techniques for each modality and is particularly advantageous when some data modalities are missing or unevenly distributed across samples.

Intermediate (or joint) fusion lies between the two extremes. Instead of merging raw input data or combining independent model predictions, this strategy involves learning a shared representation space from multiple modalities. By generating low-level joint feature embeddings that preserve signals from individual data types, intermediate fusion can improve downstream predictive tasks while maintaining modality-specific information.

Currently, there is no consensus on the superiority of any single fusion strategy. The choice is typically guided by the characteristics of the dataset (e.g., completeness, scale, noise) and the specific goals of the analysis.

An important practical challenge in multimodal modelling is resolving discordant signals between data sources — for instance, a ctDNA assay revealing a novel resistance mutation while radiomic imaging suggests disease stability. Several approaches have been proposed to address this issue. Attention-based architectures can dynamically learn which modality to "trust" more for each individual case by assigning higher weights to more informative sources according to the context. For example, the Multiple Attention Channels Aggregated Network (MACAN) architecture, used in medical imaging, employs attention mechanisms that prioritize high-quality modality signals and yield more interpretable fusion outputs [120]. Confidence-weighted fusion approaches, such as CAFusion [121], modulate each modality's influence by its estimated data quality or uncertainty at the time of analysis. This mechanism not only improves performance when data quality varies but also enables the model to down-weight potentially misleading or contradictory signals from one modality while up-weighting more reliable information from another. Hierarchical models can also prioritize signals from modalities supported by stronger clinical evidence in a given context. Qiu and colleagues applied such a framework for cancer classification using pathology and genomic features, achieving superior performance compared to state-of-the-art methods in glioma and lung cancers [122]. Incorporating these mechanisms into early, intermediate, or late fusion frameworks can help ensure that multimodal models remain robust to contradictory inputs and produce clinically meaningful outputs.

6.4. Explainable artificial intelligence (XAI)

As artificial intelligence (AI) models become increasingly integrated into clinical workflows, transparency and interpretability have become essential to ensure trust, safety, and accountability in medical decision-making. In the context of NSCLC, where treatment strategies are often life-altering, clinicians must understand how a model arrives at its predictions, especially when AI is used to guide therapy selection, predict response to treatment, or flag resistance mechanisms.

While traditional models such as logistic regression or decision trees are inherently interpretable, modern deep learning models often operate as "black boxes", making their decision logic difficult to decipher without dedicated explanation tools. Explainable AI (XAI) refers to a suite of methods and techniques designed to make the outputs of complex machine learning models understandable to human users.

XAI approaches can be broadly categorized as post-hoc explanations and intrinsically interpretable (also called ante-hoc) models [123]. Post-hoc methods analyze the decision-making process of trained models providing insights into how the models generated their predictions. For example, SHAP (SHapley Additive exPlanations), LIME (Local Interpretable Model-Agnostic Explanations), and integrated gradients approaches interpret the behavior of an already trained model by assigning feature attribution scores, highlighting the inputs most responsible for a given prediction. In contrast, intrinsic approaches are inherently interpretable models in which the explainability is built into the model architecture itself. Examples include attention-based networks, generalized additive models, and prototype-based learning frameworks.

Recent applications have demonstrated the clinical potential of XAI. Hammad and colleagues applied a custom convolutional neural network (CNN) to CT scans for lung cancer detection, using integrated gradients to generate pixel-level heatmaps that clinicians can overlay on images to validate AI-detected lesions [124]. Similarly, Wani and colleagues introduced an explainable deep-learning framework that used concept-based analysis to identify critical radiomic and clinical features driving model predictions for NSCLC diagnosis [125].

In oncology, the utility of XAI extends beyond technical transparency. Feature importance analysis can reveal biologically meaningful associations (e.g., specific mutations or immune signatures driving drug resistance), offering opportunities for biomarker discovery. Furthermore, interpretable models help clinicians validate AI outputs against known disease mechanisms, increasing the likelihood of clinical adoption.

Nonetheless, challenges persist. Explanation methods can introduce their own biases, vary depending on the underlying model, and may produce outputs that do not align with clinical reasoning. Ensuring that XAI tools are both mathematically sound and clinically meaningful remains an active area of research. It is important to emphasize that explainability is not merely a technical add-on but a prerequisite for deploying safe, trustworthy AI in precision oncology. As predictive models become more complex and multimodal, the integration of XAI techniques will be essential for their responsible, ethical, and effective use in NSCLC care.

6.5. Continual learning (CoAI)

Traditional machine learning relies on training models on static, predefined datasets. Once deployed, these models operate under the assumption that the underlying data distribution remains stable over

time. However, this paradigm does not reflect the real-world dynamics of healthcare data, particularly in oncology and pathology, where disease presentation, treatment standards, and diagnostic technologies continuously evolve. A common workaround is to periodically retrain models offline using new data, which introduce delays and requires significant computational effort. In contrast, continual learning (also referred to as continuous learning or lifelong learning) describes a framework in which models are incrementally updated as new data becomes available, without being re-trained from scratch. This approach enables AI systems to adapt to evolving patterns, such as the emergence of new biomarkers, histological transformations, and evolving therapeutic standards.

Recent reviews in medical image analysis have highlighted the growing interest and potential of continual learning to handle data drift while preserving prior knowledge [126]. For instance, Wahengbam and colleagues applied a continual learning approach to improve lung cancer diagnosis from chest X-rays and CT scans, outperforming conventional deep learning techniques [127].

Despite its promise, continual learning faces notable challenges. A major one is known as catastrophic forgetting, a phenomenon where the adaptation to new data causes the unintentional overwriting of previously acquired knowledge, resulting in reduced performance on earlier tasks or data distributions. To mitigate this, several strategies have been proposed, including regularization-based, relay-based, and optimization-based methods [128]. In addition, tracking performance over time and identifying the best version can become challenging as the continual learning models evolve. These systems may also incur higher operational costs due to increased demands on computational resources, data storage, and update orchestration.

In NSCLC and broader healthcare applications, where data shifts may be caused by changes in imaging protocols, population demographics, or treatment guidelines, continual learning holds significant potential for building robust, adaptive AI systems. However, ensuring clinical safety, regulatory compliance, and explainability during continuous updates remains an open area of research [129]. Developing scalable and interpretable continual learning frameworks will be essential to deploy trustworthy AI in dynamic clinical environments such as NSCLC care.

7. Translating AI outputs into clinical action

A critical challenge lies in translating the AI predictions into actionable clinical insights. This requires robust frameworks that connect AI outputs with decision workflows, ensure appropriate levels of therapeutic confidence, and generate evidence through clinical trial integration. In the context of NSCLC, where patient outcomes rely on precise and timely interventions, incorporating AI effectively into clinical practice demands attention to workflow usability, interpretive clarity, and regulatory alignment.

7.1. Clinical decision support workflow

AI-derived recommendations must integrate seamlessly into existing clinical workflows, delivering relevant insights at the point of care. A functional Clinical Decision Support System (CDSS) should: (1) extract and preprocess patient-specific data from diverse sources, (2) use AI models to generate interpretable predictions such as likelihood of therapeutic response or resistance, and (3) present recommendations via clinician-facing interfaces, integrated into electronic health records or treatment planning platforms.

In recent years, several CDSS solutions have been proposed to enhance decision-making quality in oncology. Among the most widely known AI-driven systems is Watson for Oncology (WFO), developed by IBM Corporation with oncologists at Memorial Sloan Kettering Cancer Center. While some studies have reported moderate to high concordance between WFO recommendations and multidisciplinary team (MDT) decisions in selected cancer types, including NSCLC [130,131], its effectiveness in improving outcomes remains under active investigation [132].

7.2. Therapeutic actionability and confidence

To be clinically useful, AI-generated recommendations in NSCLC must not only demonstrate predictive accuracy but also translate into actionable, therapeutic decisions. Increasingly, AI systems are being trained to prioritize actionable mutations, stratify patients by therapy eligibility, and suggest therapeutic combinations in alignment with evidence-based guidelines.

Assessing and communicating the level of confidence associated with each prediction is equally critical. Clinicians should know whether the model is robust or uncertain, particularly when outcomes inform potentially harmful treatment decisions, such as initiating targeted therapies or discontinuing immunotherapy. Several frameworks have emerged to address this, including the incorporation of uncertainty quantification methods (e.g., Bayesian neural networks, Monte Carlo dropout) and the integration of model calibration scores into clinical dashboards [133]. These methods enable models to estimate not only the predicted outcome but also the confidence interval surrounding it, which is essential for supporting clinician trust.

Furthermore, scaling AI recommendations to mirror established frameworks like OncoKB or the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) provides structured levels of evidence to each prediction. For instance, a detected ALK fusion might correspond to ESCAT Level 1 evidence, indicating availability of approved ALK inhibitors, whereas low-confidence or exploratory pathway interactions would receive lower tier designations. This structured annotation helps clinicians distinguish between actionable findings based on strong clinical evidence and exploratory signals warranting further validation.

Recent efforts have also focused on ensuring that model-derived actionability reflects real-world constraints, such as drug availability, local approvals, or patient-specific contraindications. For example, platforms integrating AI with real-time clinical trial databases can suggest alternative treatments or trial enrollment when standard options are not viable. While these capabilities are still evolving, early applications in NSCLC suggest the potential to support more adaptive and personalized therapeutic decision-making [134].

7.3. Clinical trial design & evidence generation

The integration of AI into clinical trial design and evidence generation has the potential to fundamentally reshape how therapeutic strategies are evaluated and translated into care. In NSCLC, where tumor heterogeneity and evolving resistance mechanisms pose substantial challenges, AI-driven tools can help stratify patients more effectively, simulate treatment outcomes, and optimize study protocols. For instance, the Watson for Clinical Trials Matching (CTM) platform applied to lung cancer increased enrollment rates by 58 % in a 2019 IASLC study following its implementation in clinical practice [135].

Adaptive trial designs powered by AI can dynamically modify key parameters (such as randomization ratios or inclusion criteria) based on interim results, accelerating the evaluation of novel therapeutics. These designs are particularly relevant for NSCLC, where biomarker-defined subgroups (e.g., EGFR-mutant, ALK-rearranged) may respond differently to treatment and evolve rapidly during therapy [136]. A prominent example is the Lung Cancer Master Protocol (Lung-MAP; S1400) in squamous NSCLC, an umbrella-trial framework which illustrates how genomic profiling and Bayesian adaptive algorithms can streamline trial efficiency and patient allocation across multiple treatment arms [137].

Furthermore, AI-generated evidence from real-world data (RWD), including de-identified EHRs, registries, and imaging repositories, is increasingly used to complement randomized controlled trials (RCTs), especially for hypothesis generation, benchmarking, and external control arms. Regulatory agencies, including the FDA and European

Medicines Agency (EMA), have increasingly recognized the potential of real-world evidence (RWE) in supporting approval decisions, particularly in oncology settings.

Nevertheless, significant challenges remain. AI-derived evidence must meet high standards of validity, transparency, and reproducibility to gain clinical and regulatory trust. Trial sponsors and regulators are now exploring how to incorporate algorithmic models into trial protocols while ensuring interpretability, bias mitigation, and auditability. Initiatives such as the Good Machine Learning Practice (GMLP) guidelines from the FDA, Health Canada, and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) aim to formalize best practices for safe AI integration in clinical development pipelines.

In NSCLC, where precision pharmacology depends on timely, biomarker-guided decisions, AI-supported trial designs and evidence-generation pipelines can significantly shorten time-to-treatment, reduce costs, and increase the relevance of findings to real-world practice. However, building trust and regulatory alignment will be essential to realize their full clinical impact.

8. Governance, ethics, and global equity

As artificial intelligence (AI) systems increasingly inform clinical decision-making in NSCLC, careful attention to governance, ethics, and equity is imperative. This section examines how data governance, regulatory frameworks, ethical oversight, and sustainability mechanisms must evolve to support the responsible deployment of AI-driven technologies in oncology.

8.1. Federated learning & data governance

Traditional centralized AI development requires pooling patient data into a single location, raising privacy, consent, and sovereignty concerns. Federated learning (FL) has emerged as a promising alternative that enables AI models to be trained across decentralized clinical sites without transferring raw data [138]. This approach is particularly relevant in NSCLC, where rare biomarkers, treatment responses, and imaging data are often distributed across institutions and countries. In fact, FL allows for collaborative model training while preserving data locality and compliance with regional privacy regulations.

Robust data governance is essential to ensure that federated infrastructures maintain security, integrity, and accountability. Standards such as the General Data Protection Regulation (GDPR) in Europe and the Health Insurance Portability and Accountability Act (HIPAA) in the United States outline strict requirements for data minimization, patient consent, and auditability. Additionally, FL systems must ensure secure aggregation, client authentication, and protection against model inversion or membership inference attacks.

Despite its promise, several challenges hinder the widespread adoption of FL in clinical research. Privacy risks remain, as sensitive information can still be inferred from gradient updates or model parameters exchanged during training. Moreover, heterogeneous data distributions across sites (non-IID data), lack of standardized preprocessing, and variable annotation quality can degrade model performance. Finally, explainability is often more difficult to achieve in FL settings, since developers may not have access to raw input data or local context, complicating model validation and interpretation [139].

8.2. Regulatory pathways & post-market surveillance

AI technologies in oncology must navigate evolving regulatory pathways that balance innovation with patient safety. The FDA, EMA, and other authorities have issued initial frameworks for AI/ML-based Software as a Medical Device (SaMD). These include guidelines on algorithm transparency, validation across populations, and lifecycle management.

A particular challenge for adaptive AI systems is post-market surveillance. Unlike static models, continuously learning algorithms may change over time, potentially altering clinical behavior. Regulatory strategies such as the "Predetermined Change Control Plan", proposed by FDA, Health Canada, and MHRA, aim to allow for model updates within pre-approved boundaries while requiring real-world performance monitoring. For NSCLC, where rapid shifts in standard-of-care occur, dynamic oversight models will be necessary to track effectiveness, flag safety concerns, and ensure algorithmic accountability.

8.3. Ethical, legal and social implications

The use of AI in NSCLC raises complex ethical and legal questions. Ensuring algorithmic fairness is paramount to prevent reinforcing existing disparities in cancer care. If training datasets underrepresent certain racial, ethnic, or gender groups, models may systematically underperform for those populations. Equity audits, bias mitigation techniques, and participatory design approaches involving diverse stakeholders must be integrated into the development process.

Furthermore, legal liability in cases of AI-driven misdiagnosis or inappropriate treatment recommendations remains unresolved. Clinician-AI interaction frameworks must clarify where responsibility lies and how explainability tools can support informed clinical judgment. Social implications also extend to patient autonomy and informed consent: patients should be made aware when AI contributes to clinical decisions and what that entails for their care.

8.4. Long-term sustainability

The long-term success of AI in NSCLC depends on sustainability, technically, economically, and institutionally. Models must be maintained, recalibrated, and periodically audited for performance drift. Open-source frameworks and public-private consortia may support long-term stewardship, especially in low-resource settings.

Economically, reimbursement models that recognize the value of AI-enabled diagnostics and treatment planning will be essential to drive adoption. Initiatives such as value-based pricing, outcome-linked payments, or bundled reimbursement schemes may be needed.

Finally, global equity must be a central consideration. Many low- and middle-income countries (LMICs) face infrastructural barriers to deploying advanced AI systems. Supporting scalable, interpretable, and resource-aware AI tools, potentially built on federated networks, can democratize access to cutting-edge cancer care. International collaboration and capacity building will be key to ensuring AI benefits all patients, regardless of geography.

9. Conclusions and future perspectives

The therapeutic landscape of NSCLC is becoming increasingly complex since pharmacological pressure may induce acquired resistance driven by complex genetic and epigenetic changes that need to be predicted before disease progression for effective management. Treatment decisions are increasingly driven by druggable mutations and biomarkers associated with response to approved first-line therapies, fundamental components of current guidelines.

Molecular Tumor Boards (MTBs) or expert clinicians are responsible for selecting alternative treatment strategies for candidate patients who have failed (or are expected to fail) standard therapies or have limited options. The advent of AI, particularly advanced deep learning models, presents an extraordinary opportunity to develop algorithms capable of decoding the complex multifaceted patterns of NSCLC progression, helping clinicians in complex decision-making processes. Since the predictive power of AI models is related to the abundance of high-quality data, it is pivotal to have comprehensive and heterogeneous datasets. Data may come from medical records, international guidelines for approved drugs, clinical trials for investigational new drugs, and real-world information based on longitudinal monitoring of disease

evolution, including NGS assays on liquid biopsy and radiomic features.

A key question is how AI can be integrated into real-world NSCLC scenarios. Traditionally, clinical follow-up adopts a "reactive approach", where treatments are switched upon evidence of disease progression or unacceptable toxicity (Fig. 2). In this context, a more comprehensive analysis of the mutational burden via AI — leveraging NGS, radiomics, druggable target maps (OncoKB, ESCAT), real-time clinical trial databases, and correlations with patient's clinical features — could lead to the identification of resistance mechanisms thus suggesting next-line therapies, including approved treatments, out-of-class drugs, or previously unconsidered existing drugs that may target resistance pathways (drug repurposing) (Fig. 2). AI-derived outputs should be reviewed by a Clinical Decision Support System (CDSS) team and subsequently validated by MTBs or NSCLC expert clinicians, ensuring that algorithmic recommendations translate into clinically actionable strategies. This may result in a more effective and personalized therapy for the patient or in a proof of concept that stimulates innovative clinical trials. While promising, this reactive paradigm may suffer from the delay of clinical evidence concerning the early molecular switch that characterizes tumor evolution, making therapeutic choices sometimes late and inadequate.

In contrast, a proactive follow-up (Fig. 2) may form the basis of a predictive medical approach based on non-invasive methods (e.g., ctDNA CT scan) to analyze tumor changes that occur in acquired secondary or tertiary resistance. This will allow clinicians to predict, before disease progression, whether the treatment plan needs to be changed. AI systems may learn from longitudinal multimodal data to offer dynamic, patient-specific therapeutic plans that anticipate progression, predict disease trajectories, and enable real-time treatment personalization (Fig. 2). For instance, in lung cancer, a combination of AI technology and CT images was carried out to develop a personalized non-invasive biomarker able to distinguish high-TMB from low-TMB, which can help clinicians make decisions on the use of ICIs in patients with advanced NSCLC [4]. Another study used an 18F-FDG-PET/CT-based deep learning model for the quantification of EGFR mutation status in NSCLC patients. The authors showed that the AI-derived score was positively associated with longer PFS in patients treated with EGFR TKIs and negatively associated with higher durable clinical response, reduced hyperprogression, and longer PFS among patients treated with ICIs [53]. Overcoming the standard manual assessment can be challenging, especially for immunotherapies where patterns of disease progression can be atypical. The large dataset from dynamic disease monitoring (e.g., plasma NGS and/or CT scan) could be processed and matched with clinical features and druggable target information using the AI-derived model. For example, a machine learning approach was found to predict PFS after chemotherapy, targeted therapy, or immunotherapy using quantitative features from longitudinal CT scans of NSCLC patients [52].

Together, these applications underscore the potential of an AI-driven multimodal pharmacological approach for NSCLC to support both reactive and proactive clinical decision-making. By identifying resistance mechanisms and choosing personalized next-line therapies AI may transform clinical outcomes.

In addition, AI is increasingly recognized as a valuable tool in clinical trial design [140]. AI-generated recommendations based on real-world data (Fig. 2) can support trial design and adaptation, patient stratification, and toxicity prediction. The resulting real-world evidence – such as safety outcomes and treatment responses – could serve as a basis for retraining AI models, thus improving their predictive accuracy and ensuring alignment with emerging clinical and pharmacovigilance data. In line with this concept, there is evidence showing the application of AI to predict the toxicity profiles of checkpoint inhibitor immunotherapy at the population level [141]. Continuous model retraining is also imperative to parallel the evolving scientific knowledge and technological advancements, thus ensuring that predictive algorithms align with emerging insight into NSCLC biology and therapeutic modalities. Finally, explainable AI techniques should be adopted to ensure transparency and impartiality in decision-making, essential aspects for clinicians to trust and adopt AI recommendations.

Future perspectives entail the establishment of a central data repository with restricted access to accredited MTB and CDSS members or Institutions. This initiative would facilitate the transition from local to global predictive models, enabling collaborative decision-making on a broader scale. Privacy limitations can be overcome through federated learning methodologies, wherein model training occurs on decentralized data sources without compromising data security. Leveraging this approach may enable the identification of innovative therapeutic strategies tailored to individual patient profiles, thus offering cancer patients worldwide an opportunity for long-term, quality-adjusted survival through shared treatment plans.

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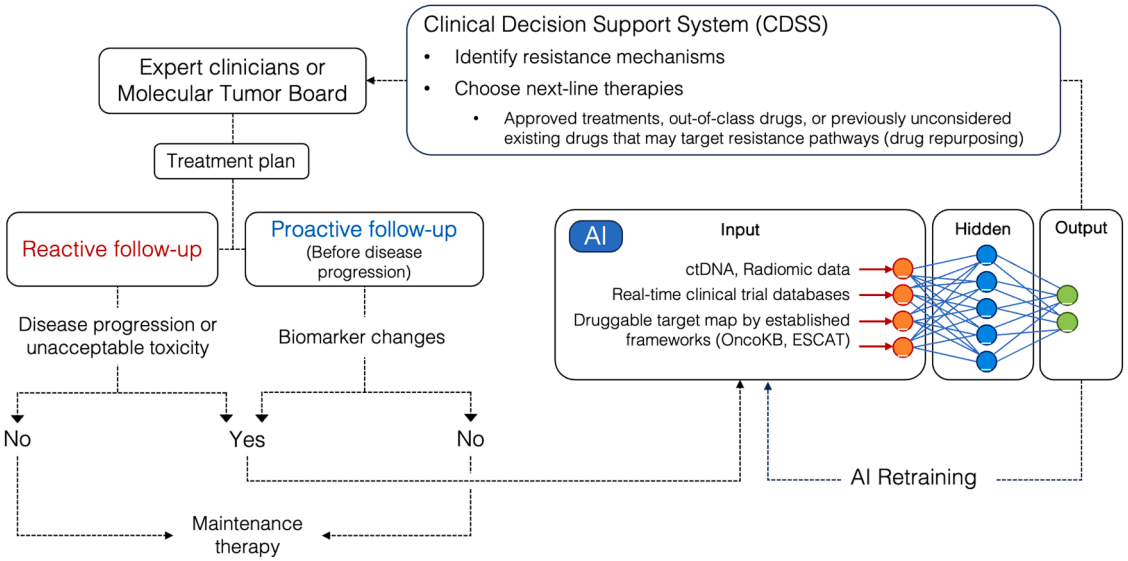

Fig. 2. Artificial intelligence (AI)-based algorithms in the reactive and proactive scenarios for treatment optimization in non-small-cell lung cancer.

CRediT authorship contribution statement

Stefano Fogli: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Alessandro Barberis:** Writing – review & editing, Conceptualization. **Marzia Del Re:** Writing – review & editing, Visualization, Conceptualization. **Stefania Crucitta:** Writing – review & editing, Investigation. **Martina Ruglioni:** Writing – review & editing, Investigation. **Giovanna Luculli:** Writing – review & editing, Investigation. **Giorgio Guglielmi:** Writing – review & editing, Investigation. **Cristina Scavone:** Investigation. **Iacopo Petrini:** Investigation. **Nicola Panzeri:** Writing – review & editing, Conceptualization. **Andrea Pierini:** Writing – review & editing, Conceptualization. **Christian Rolfo:** Writing – review & editing, Investigation, Conceptualization. **Romano Danesi:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

Stefano Fogli: Pfizer, Novartis, Roche, BMS, Lilly, Teva, Janssen, Celgene (scientific advisory board, consulting relationship, travel expenses); Marzia Del *Re*: Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Pierre-Fabre, Janssen (scientific advisory board, consulting relationship), Ipsen, AstraZeneca, Sanofi Genzyme (travel, accommodation, expenses); Alessandro Barberis: none; Stefania Crucitta: none; Martina Ruglioni: none; Giovanna Luculli: none; Giorgio Guglielmi: none; Cristina Scavone: none; Iacopo Petrini: none; Nicola Panzeri: Roche (employee, Integrated Access); Andrea Pierini: Roche (employee, Integrated Access); Christian Rolfo: none; Romano Danesi: Roche, Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Janssen, Gilead, Lilly, Gilead, EUSA Pharma (scientific advisory board, consulting relationship), Ipsen, Sanofi Genzyme (travel, accommodation, expenses).

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