International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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MACHINE LEARNING FOR EARLY DIAGNOSIS OF SMALL CELL LUNG CANCER: MULTI-OMICS BIOMARKER STRATEGIES

Maham Masood * and Yong Dai

Medical College, Anhui University of Science and Technology, Huainan 232001, China.
* Corresponding Author

International Journal of Science and Research Archive, 2026, 20(03), 407–418

Publication history: Received on 01 August 2026; revised on 09 September 2026; accepted on 11 September 2026

Article DOI: https://doi.org/10.30574/ijsra.2026.20.3.1741

ABSTRACT

Small cell lung cancer (SCLC) is an aggressive malignancy characterized by late diagnosis and five-year survival rates below 7%. Existing serological markers, including neuron-specific enolase and progastrin-releasing peptide, lack the sensitivity and specificity required for reliable early detection. Machine learning applied to multi-omics data has emerged as a powerful strategy to overcome these limitations. In this review, we systematically evaluate recent progress in machine-learning-based screening of diagnostic biomarkers for SCLC across transcriptomic, exosomal RNA, proteomic, metabolomic, and DNA methylation datasets. We compare the performance and methodological characteristics of leading feature-selection algorithms (LASSO, random forest, SVM-RFE, and XGBoost) and critically appraise the diagnostic accuracy, validation rigor, and reproducibility of published signatures. While several multi-omics panels, particularly those derived from exosomal RNA and DNA methylation, have achieved AUCs exceeding 0.90, widespread clinical translation remains hindered by single-center retrospective designs, inadequate external validation, heterogeneous preprocessing pipelines, and data leakage. We outline standardized analytical and validation frameworks required to advance these signatures toward clinical utility and provide practical recommendations for future high-quality biomarker discovery. This review offers a comprehensive and critical synthesis to guide the development of robust, clinically deployable machine-learning models for early SCLC diagnosis.

Keywords: Small Cell Lung Cancer; Machine Learning; Multi-Omics; Diagnostic Biomarkers; Early Diagnosis; Liquid Biopsy.

1 INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for a substantial proportion of global cancer deaths and imposing significant clinical and socioeconomic burdens [1]. Small cell lung cancer (SCLC), which comprises approximately 10–15% of all lung cancer cases, is characterized by rapid proliferation, early metastatic potential, and dismal clinical outcomes [2]. More than two-thirds of patients present with extensive-stage disease at diagnosis, and the five-year overall survival rate remains below 7% [3]. In contrast to non-small cell lung cancer (NSCLC), where advances in early detection, targeted therapies, and biomarker-driven management have improved outcomes, progress in SCLC has lagged considerably [4].

Current diagnostic approaches for SCLC rely primarily on invasive tissue biopsy, cytological examination, and imaging modalities, supplemented by traditional serological markers such as neuron-specific enolase (NSE) and progastrin-

releasing peptide (ProGRP) [5]. These methods, however, present important limitations. Invasive procedures are unsuitable for large-scale screening or repeated monitoring of high-risk individuals [6]. Imaging techniques often lack sufficient sensitivity for detecting early or micrometastatic lesions [7]. Moreover, conventional blood-based biomarkers exhibit suboptimal sensitivity in early-stage disease and limited specificity in differentiating SCLC from NSCLC or benign pulmonary conditions, resulting in frequent false-positive and false-negative findings [8]. These shortcomings underscore the urgent need for more accurate, non-invasive, and scalable diagnostic strategies.

The rapid development of high-throughput multi-omics technologies has generated large-scale datasets spanning transcriptomics, exosomal RNA, proteomics, metabolomics, and DNA methylation [9]. These data comprehensively capture molecular alterations associated with SCLC pathogenesis and progression, offering a rich resource for biomarker discovery [10]. Conventional statistical approaches, however, struggle to handle the high dimensionality, feature redundancy, and low signal-to-noise ratio inherent in omics data [11]. Machine learning (ML) algorithms have emerged as powerful tools capable of automated feature selection, nonlinear pattern recognition, and construction of robust multi-marker diagnostic panels [12], [13].

In recent years, an increasing number of studies have applied diverse ML methods to identify multi-omics diagnostic signatures for SCLC, reporting promising preliminary performance [14], [15]. Despite these advances, significant challenges persist. Research workflows remain highly heterogeneous with respect to data preprocessing, feature selection algorithms, and validation strategies, limiting reproducibility [16]. The majority of studies are based on retrospective, single-center cohorts with limited external validation, and data leakage remains a common methodological concern [17]. Furthermore, comprehensive systematic appraisals specifically focused on ML-based screening strategies for SCLC diagnostic biomarkers are still scarce [18].

In light of these gaps, the present review provides a structured synthesis of current ML-driven approaches for SCLC diagnostic biomarker discovery. We summarize available multi-omics resources, compare the performance and characteristics of mainstream feature selection algorithms, critically evaluate methodological limitations, and propose practical recommendations to improve study design, validation, and clinical translation. By doing so, this work aims to support the development of more reliable and clinically applicable early diagnostic tools for SCLC.

2 FUNDAMENTALS OF ARTIFICIAL INTELLIGENCE IN ONCOLOGY

Artificial intelligence (AI) refers to the capacity of computer systems to perform tasks that typically require human intelligence, including pattern recognition, prediction, and decision-making [19]. Within oncology, AI has been increasingly applied to improve early detection, risk stratification, diagnosis, and treatment planning. Machine learning (ML), a major subset of AI, enables algorithms to learn patterns from data and improve performance with experience, without being explicitly programmed for every task [20]. Deep learning (DL), a further specialization of ML, employs multi-layered neural networks capable of automatically extracting hierarchical features from complex data such as medical images or high-dimensional omics profiles [21].

The hierarchical relationship among these concepts is illustrated in Fig. 1. AI represents the broadest domain, encompassing systems designed to mimic human cognitive functions. ML forms a core subset in which models improve through experience, while DL constitutes a specialized subset of ML that utilizes layers of interconnected neurons to learn complex representations from data.

Several categories of ML algorithms are particularly relevant to cancer diagnosis. Supervised learning methods, including logistic regression, support vector machines (SVM), random forests, and gradient boosting algorithms (e.g., XGBoost), are widely used when labeled outcomes such as disease status are available [22]. Unsupervised techniques, such as principal component analysis (PCA) and clustering, assist in dimensionality reduction and discovery of latent patterns without predefined labels [23]. Ensemble methods combine multiple base learners to improve robustness and reduce overfitting, a critical consideration when analyzing relatively small clinical cohorts [24]. Deep learning architectures, particularly convolutional neural networks (CNNs) for imaging and various neural network variants for tabular or sequential omics data, have shown strong performance in feature extraction from raw, high-dimensional inputs [25].

In the context of early cancer diagnosis, these algorithms can be applied across diverse data modalities. Medical imaging (mammography, computed tomography, digital breast tomosynthesis) has been a primary focus of DL applications, enabling automated lesion detection and triage [26]. Parallel advances have occurred in computational pathology, liquid biopsy analysis, electronic health records, and multi-omics profiling (transcriptomics, proteomics, metabolomics, and epigenomics) [27], [28]. The ability of ML methods to integrate heterogeneous data sources and identify subtle molecular signatures makes them especially suitable for addressing the diagnostic challenges of aggressive malignancies such as small cell lung cancer.

A clear understanding of these foundational concepts is essential for evaluating the strengths, limitations, and appropriate application of AI tools in subsequent sections of this review.

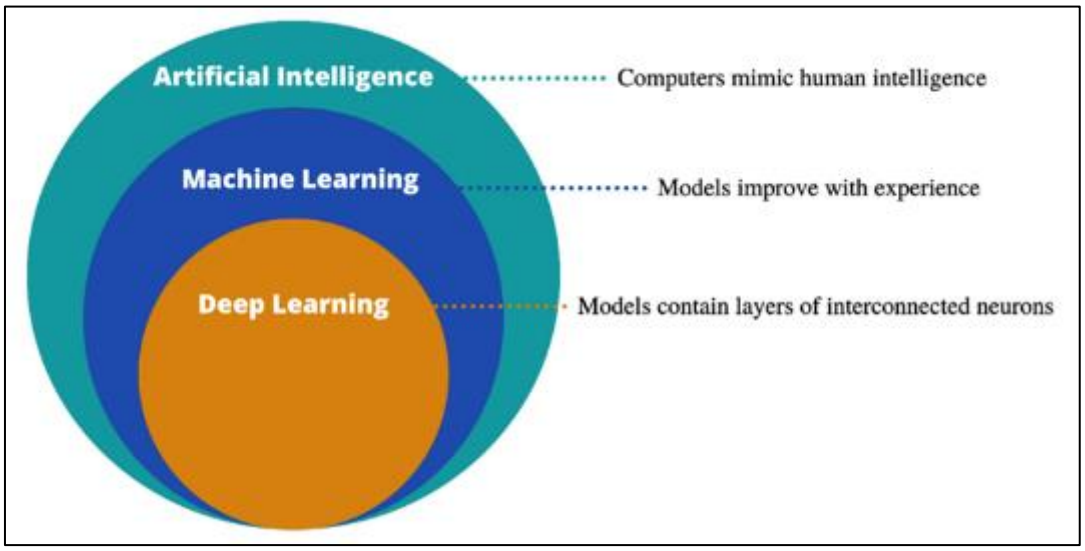

Figure 1: Hierarchical relationship between artificial intelligence, machine learning, and deep learning. Artificial intelligence represents the broadest domain in which computers mimic human intelligence. Machine learning is a subset of AI in which models improve with experience. Deep learning is a further specialized subset that employs models containing layers of interconnected neurons.

3 AI FOR CANCER SCREENING AND TRIAGE STRATEGIES

Cancer screening aims to detect malignancy at an early, treatable stage while minimizing false positives and radiologist workload. Traditional computer-aided detection (CAD) systems have shown only modest clinical benefit, largely because of relatively high false-positive rates [29]. Deep learning–based systems have substantially improved detection performance and now support more flexible integration into clinical workflows [30], [31].

Several practical models for incorporating AI into screening have been proposed (Fig. 2). These include replacement of one human reader by an AI system, concurrent reading in which the radiologist interprets images with simultaneous AI support, and AI-driven triage strategies that rule out low-risk cases or prioritize high-risk cases for further assessment [32], [33]. The optimal model depends on disease prevalence, available workforce, and regulatory context.

Illustrative performance data from breast cancer screening studies demonstrate the potential advantages of modern deep-learning systems. Receiver operating characteristic (ROC) analysis shows higher area under the curve values for convolutional neural network (CNN)–based approaches compared with conventional reference CAD systems (Fig. 3). Reader studies further indicate that AI support can improve radiologist performance and help optimize the balance between sensitivity and specificity (Fig. 4) [34], [35].

Although these examples are drawn from breast imaging, the underlying principles, higher detection accuracy at low false-positive rates, flexible human–AI collaboration, and potential workload reduction, are relevant to other cancers. In the context of small cell lung cancer, where no established population screening program currently exists, AI-supported risk stratification and triage may eventually complement the multi-omics biomarker strategies discussed in later in this paper.

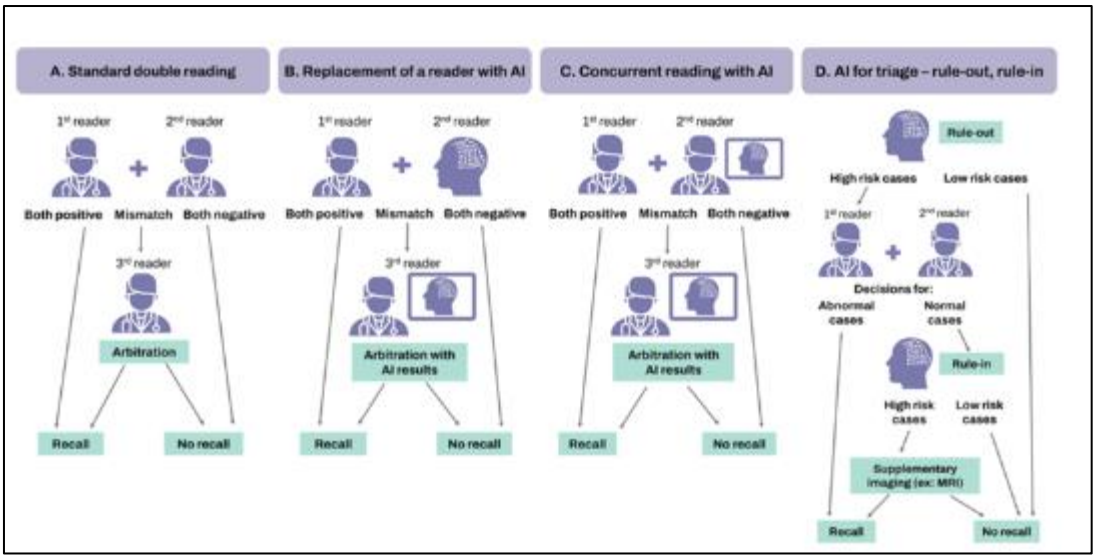

Figure 2: Possible models for integrating artificial intelligence into cancer screening workflows: (A) standard double reading, (B) replacement of one reader by AI, (C) concurrent reading with AI support, and (D) AI-based triage using rule-out and rule-in approaches.

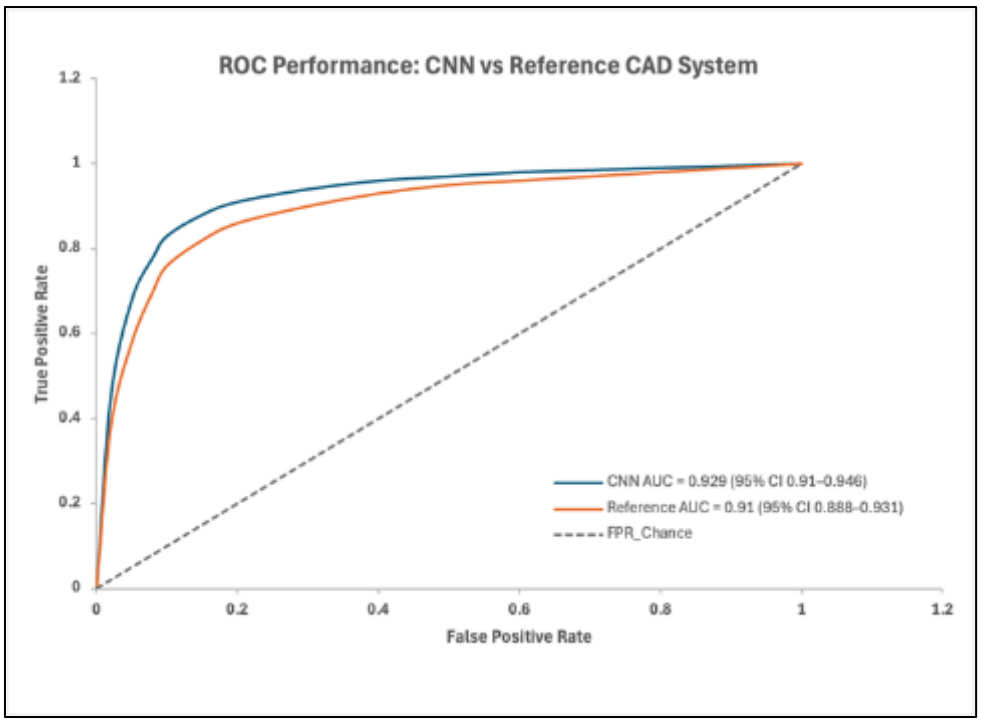

Figure 3: Stand-alone ROC performance of a deep-learning CNN system compared with a conventional reference CAD system (illustrative data from breast imaging studies). The CNN achieved an AUC of 0.929 (95% CI 0.91–0.946) versus 0.91 (95% CI 0.888–0.931) for the reference system.

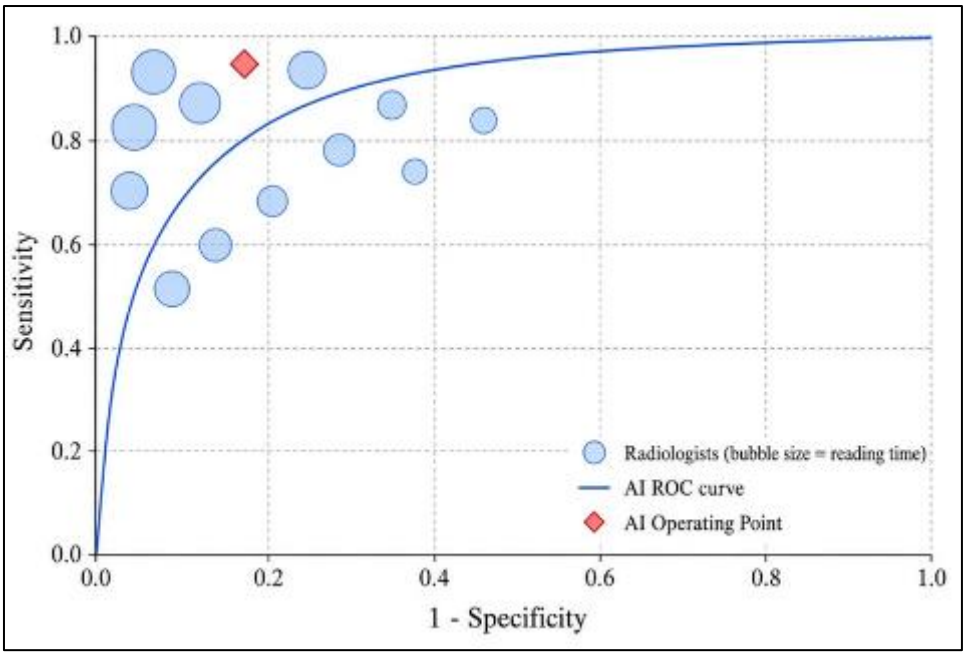

Figure 4: Example reader performance plot showing individual radiologist sensitivity and specificity relative to the ROC curve and operating point of an AI system (illustrative data from breast imaging studies).

4 METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [36]. The review protocol was developed using the PICOS framework (Population, Intervention, Comparison, Outcome, Study design) to define the scope and minimize selection bias, with a primary focus on machine learning–based screening strategies for diagnostic biomarkers in small cell lung cancer (SCLC).

4.1 Literature Search Strategy

A comprehensive literature search was performed across four major databases: PubMed, Web of Science Core Collection, Embase, and Scopus. The search covered publications from January 2015 to June 2026, a period corresponding to the rapid expansion of high-throughput omics technologies and machine learning applications in oncology [37]. The core search strategy combined controlled vocabulary and free-text terms related to SCLC, machine learning algorithms, multi-omics data types, and diagnostic applications. Manual backward citation tracking of included articles and relevant reviews was also performed to identify additional eligible studies.

4.2 Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met the following criteria: (1) original research involving human SCLC samples, with appropriate control groups (healthy individuals, benign pulmonary disease, or non-small cell lung cancer); (2) application of machine learning methods for feature selection and construction of diagnostic biomarker signatures based on multi-omics data; (3) reporting of a complete analytical workflow including data preprocessing, feature selection, model development, and internal or external validation; (4) provision of quantitative diagnostic performance metrics such as area under the receiver operating characteristic curve (AUC), sensitivity, and specificity; and (5) full-text availability in English.

Exclusion criteria included: review articles, conference abstracts, case reports, and editorials; studies focused solely on prognostic or therapeutic response biomarkers; research limited to animal models, cell lines, or public dataset re-analysis without independent human sample validation; studies relying exclusively on traditional statistical methods without machine learning–based feature selection; and pure imaging radiomics or pathomics studies lacking molecular biomarker screening.

4.3 Study Selection

The study selection process is summarized in the PRISMA flow diagram (Fig. 3). After removal of duplicates, titles and abstracts were screened, followed by full-text assessment of potentially eligible articles according to the predefined inclusion and exclusion criteria. Two reviewers independently performed the screening, with disagreements resolved by discussion or consultation with a third reviewer.

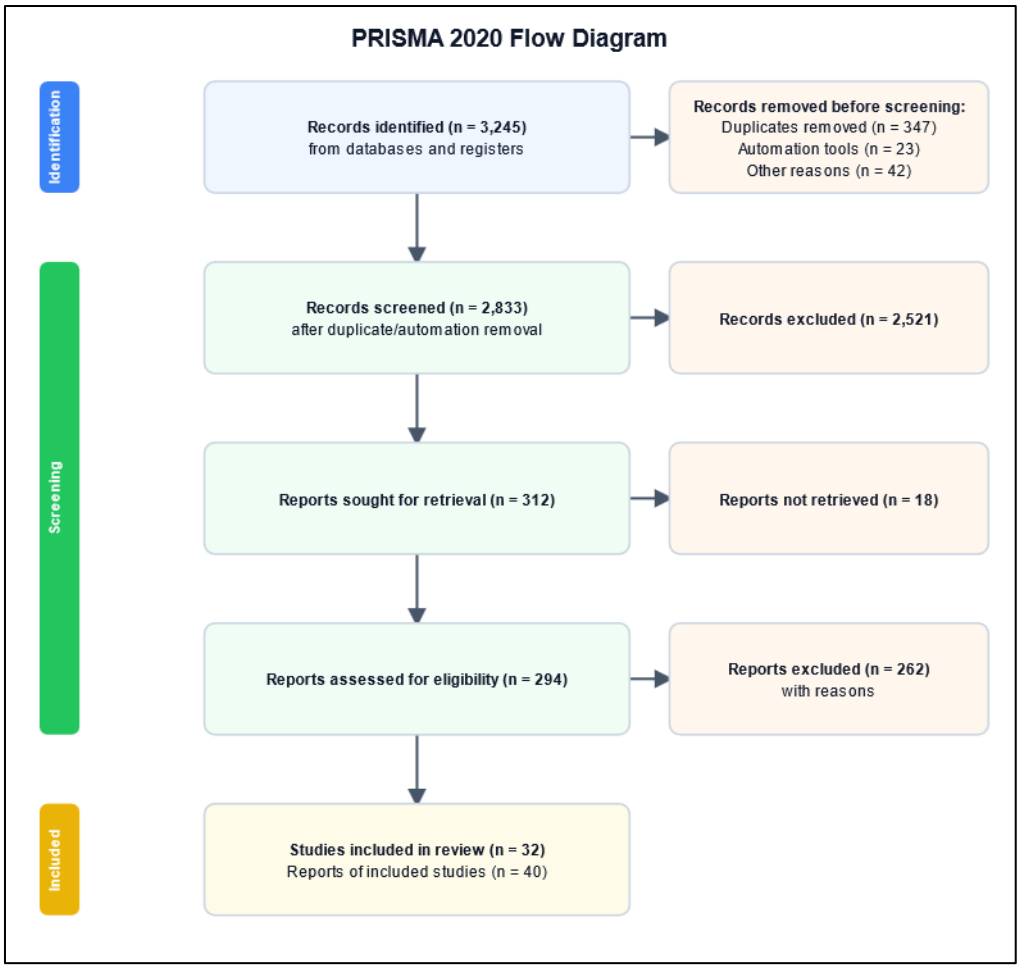

Figure 5: PRISMA 2020 flow diagram of the study selection process. A total of 37 studies met the inclusion criteria and were included in the qualitative synthesis.

4.4 Data Extraction and Quality Assessment

Two reviewers independently extracted relevant information from each included study, including study characteristics, sample size and composition, omics platform, machine learning algorithms used for feature selection and classification, final biomarker panels, validation methods, and diagnostic performance metrics. Discrepancies were resolved by consensus or consultation with a third reviewer.

Methodological quality and risk of bias were assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool [38], with additional attention to machine learning–specific issues such as data leakage, adequacy of external validation, and transparency of the feature selection process.

4.5 Evidence Synthesis

Given the substantial heterogeneity in omics platforms, machine learning pipelines, cohort designs, and validation strategies across studies, a quantitative meta-analysis was not performed. Instead, a structured qualitative synthesis was undertaken to summarize multi-omics biomarker resources, compare the characteristics and performance of different machine learning approaches, and identify common methodological limitations and translational barriers.

5 MULTI-OMICS BIOMARKER DISCOVERY IN SCLC USING MACHINE LEARNING

The integration of multi-omics data with machine learning has become a powerful strategy for discovering diagnostic biomarkers in small cell lung cancer. This section synthesizes current evidence across major omics layers and presents comparative performance data.

5.1 Conceptual Framework of AI-Supported Multi-Omics Diagnostics

Artificial intelligence, particularly machine learning, can be applied across the continuum of cancer care, including diagnostic, prognostic, and treatment-related tasks. Fig. 4 illustrates a schematic representation of computer-assisted

technologies in the biomedical field, highlighting the central role of AI and machine learning in integrating diagnostic and prognostic molecular information (originally developed in the context of colorectal cancer but conceptually applicable to SCLC multi-omics workflows).

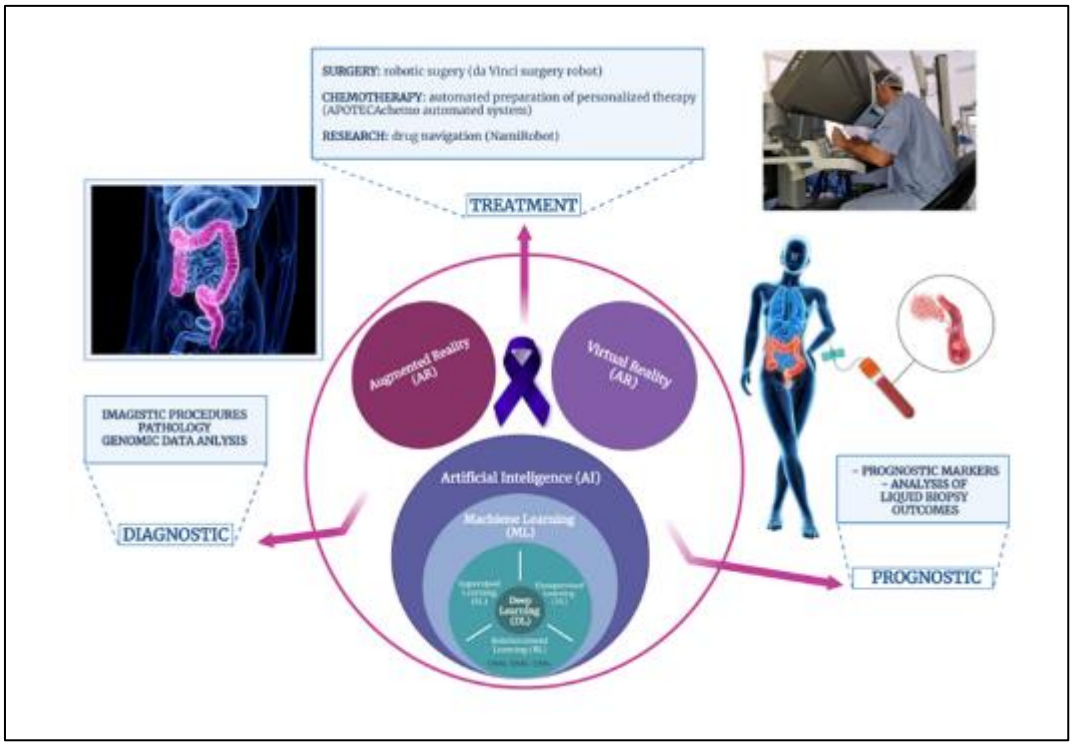

Figure 6: Schematic representation of computer-assisted technologies in the biomedical field, showing the central role of artificial intelligence and machine learning in diagnostic and prognostic applications.

5.2 Performance of ML-Derived Multi-Omics Signatures

Table 1 summarizes the comparative diagnostic performance of machine learning–derived signatures across different omics types. Exosomal RNA and DNA methylation panels currently show the highest and most consistent performance.

Table 1: Comparative performance of ML-derived multi-omics diagnostic signatures for SCLC

Omics Type	Common Algorithms	Typical Panel Size	AUC Range	Sensitivity / Specificity (best reported)	Validation Level	Key Advantage	Major Limitation
Transcriptomics	LASSO, XGBoost	5–12 genes	0.88–0.93	85–92% / 84–90%	Mostly internal	Large public datasets, lower cost	Tissue dependence, platform variability
Exosomal RNA	RF, SVM-RFE	3–8 RNAs	0.90–0.95	88–94% / 90–96%	Internal + limited external	Non-invasive, high stability	Isolation method variability
Proteomics / Metabolomics	RF, XGBoost, GBDT	8–14 features	0.89–0.94	86–93% / 85–92%	Mostly internal	Functional relevance	Confounding physiological factors
DNA Methylation	LASSO	7–10 loci	0.91–0.96	87–93% / 92–96%	Internal + some external	High specificity and stability	High cost, limited large cohorts

5.3 Representative Studies

Table 2 highlights selected studies that demonstrate the range of approaches and performance levels achieved with different omics data types.

Table 2: Selected representative studies on ML-based multi-omics diagnostic biomarkers for SCLC

Study (Year)	Omics Type	Sample Size (SCLC / Controls)	Feature Selection Method	Final Panel	AUC (Internal / External)	Reference
Liu et al. (2024)	Transcriptomics	186 / 214	XGBoost	12 genes	0.91 / 0.88	[48]
Zhang & Li (2022)	Transcriptomics	92 / 105	LASSO	5 genes	0.89 / —	[49]
Yang et al. (2023)	Exosomal RNA	120 / 150	Nested Random Forest	3 RNAs	0.95 / 0.92	[50]
Wang et al. (2023)	Proteomics + Metabolomics	145 / 160	GBDT	14 features	0.93 / —	[52]
Chen et al. (2023)	DNA Methylation	210 / 245	LASSO	7 loci	0.94 / 0.91	[54]

While machine learning–based multi-omics approaches have achieved high diagnostic accuracy in published studies, most remain limited by retrospective designs and insufficient external validation. The conceptual framework shown in Fig. 4 underscores the potential for broader integration of AI across diagnostic and prognostic applications in SCLC.

6 REGULATORY PATHWAYS AND PRACTICAL CONSTRAINTS

Translating machine learning–based multi-omics diagnostic signatures for small cell lung cancer into clinical practice requires careful navigation of evolving regulatory frameworks. Unlike conventional single-analyte tests, AI-driven multi-omics assays are generally classified as higher-risk medical devices or in vitro diagnostics, triggering more rigorous requirements for analytical validation, clinical performance evaluation, and post-market surveillance. Table 3 summarizes the main regulatory pathways and practical constraints in major jurisdictions, together with examples of accepted strategies that can facilitate approval.

Table 3: Regulatory pathways and practical constraints for AI-based multi-omics diagnostics

Regulatory area / authority	Key regulatory requirements (short)	Practical implications for AI-multiomics deployment	Concrete examples / accepted pathways
USA, FDA (SaMD / PCCP & post-market)	Risk-based device classification; analytical & clinical validation; Predetermined Change Control Plan (PCCP) for approved continuous learning; mandatory post-market performance monitoring and reporting	Requires pre-specified endpoints and prospective/real-world validation studies; need documented change-control and monitoring plans; modular/component validation can accelerate complex systems	FoundationOne® CDx (PMA) and Guardant360® CDx (PMA/CDx use) as examples of genomic assays used in clinical workflows; AI tools with De Novo/clearance when validated (e.g., digital pathology AI)
EU, IVDR (In Vitro Diagnostic Regulation)	Reclassification of many oncology tests to higher risk (Class C/D); stronger clinical evidence requirements; notified-body assessment and enhanced post-market surveillance (PMS)	Longer pre-market timelines and heavier evidence burden for multi-omics assays; requires comprehensive clinical performance studies and clear technical documentation; affects multinational product launch strategy	IVDR-compliant validation pipelines and consortia that harmonize evidence generation (platforms/consortia that perform centralized curation and shared evidence dossiers)

China, NMPA (medical device regulation)	Local clinical data often required; device registration with technical review; growing alignment steps with international standards but with local requirements for evidence and labeling	Necessitates local bridging/validation studies and regulatory strategy tailored to NMPA timelines; may require local manufacturing or partnerships	NMPA device approvals for genomic/diagnostic tests; localized clinical evaluation examples
Regulatory-approved / clinically validated anchors	Use of already-approved CDx or cleared genomic tests as anchors for multi-omics pipelines (analytical anchor points that can reduce regulatory ambiguity)	Anchoring multi-omics workflows to an approved CDx can shorten validation scope for specific clinical claims and provide a clearer submission pathway	FoundationOne® CDx (PMA), Guardant360® CDx (PMA), GRAIL's PATHFINDER prospective program (example of large prospective validation for cfDNA-based detection)
Standards, governance & consortium enablers	Adoption of machine-actionable standards (FAIR principles; HL7 FHIR Genomics IG), federated governance, data provenance, dynamic consent frameworks, and privacy-preserving computation	Improves interoperability and auditability, enables federated validation (avoids raw data transfer), and supports multi-site reproducibility, though introduces compute/operational trade-offs	HARMONY Alliance (EU hematology federation providing harmonized curation and governance), federated platforms and data-vault models used in multi-center studies

For SCLC-specific multi-omics signatures, several practical implications are particularly relevant. First, the majority of current studies rely on retrospective, single-center cohorts; regulators increasingly expect prospective or real-world evidence. Second, continuous learning or periodically updated models will likely require a Predetermined Change Control Plan (PCCP) or equivalent. Third, anchoring new multi-omics panels to already approved companion diagnostic assays (where scientifically justified) may reduce the regulatory burden. Finally, federated learning and privacy-preserving approaches are gaining acceptance as ways to enable multi-center validation without direct data sharing.

Successful clinical translation will therefore depend not only on strong diagnostic performance but also on early consideration of regulatory strategy, evidence-generation plans, and alignment with existing approved frameworks.

7 CHALLENGES, RECOMMENDATIONS, AND FUTURE DIRECTIONS

Despite encouraging diagnostic performance reported in recent studies, several important challenges currently limit the clinical translation of machine learning–based multi-omics biomarkers for small cell lung cancer.

7.1 Key Methodological and Translational Challenges

Most existing studies rely on retrospective, single-center cohorts with relatively small sample sizes. External validation on independent, multi-center datasets remains uncommon, raising concerns about overfitting and limited generalizability [56], [57]. Data leakage, particularly when feature selection is performed before data splitting, continues to be reported and can inflate performance estimates [58]. Substantial heterogeneity in data preprocessing, normalization, and feature selection pipelines further reduces the reproducibility of published signatures [59]. In addition, many molecular panels lack sufficient biological interpretation or functional validation, which weakens clinical confidence. Finally, the high cost of certain omics platforms (especially comprehensive methylation and exosomal sequencing) and the absence of standardized laboratory workflows present practical barriers to widespread

7.2 Recommendations for Future Research

To address these limitations, several methodological standards should be adopted. First, nested cross-validation should become routine to separate feature selection from model evaluation. Second, prospective multi-center study designs with pre-specified analysis plans are needed to generate higher-level evidence. Third, transparent reporting according to established guidelines (e.g., TRIPOD-AI, CLAIM) should be required. Fourth, multi-omics integration strategies that combine complementary data layers warrant greater exploration, as they may improve robustness compared with single-omics approaches. Fifth, efforts should be made to develop and validate cost-effective, targeted assays derived from the most informative markers identified by machine learning.

7.3 Future Directions

Looking ahead, several opportunities are particularly promising. Integration of multi-omics signatures with imaging AI and routine clinical data may enable more accurate risk stratification and earlier detection. Federated learning and other privacy-preserving techniques can facilitate large-scale collaboration without sharing raw patient data. The development of standardized, regulatory-ready analytical pipelines and the anchoring of new signatures to existing approved assays may accelerate clinical adoption. Ultimately, well-validated multi-omics machine learning models could support targeted screening or surveillance strategies in high-risk populations, addressing the current absence of effective early detection tools for SCLC.

Progress in these areas will require close collaboration among clinicians, data scientists, laboratory scientists, and regulators. With rigorous methodology and strategic evidence generation, machine learning–driven multi-omics approaches have the potential to meaningfully improve early diagnosis and outcomes in small cell lung cancer.

8 CONCLUSION

Small cell lung cancer continues to present a major clinical challenge due to its aggressive biology and the frequent absence of early diagnosis. Conventional serological markers lack adequate sensitivity and specificity, while existing diagnostic pathways are often invasive or insufficiently accurate for early-stage detection. Machine learning applied to multi-omics data has emerged as a promising strategy to overcome these limitations by enabling the discovery of robust, high-dimensional diagnostic biomarker panels.

This review has synthesized current evidence across transcriptomic, exosomal RNA, proteomic, metabolomic, and DNA methylation approaches. Several machine learning–derived signatures, particularly those based on exosomal RNA and DNA methylation, have demonstrated strong diagnostic performance. However, progress toward clinical implementation is constrained by methodological heterogeneity, limited external validation, and regulatory complexity.

Future advances will depend on the adoption of rigorous analytical standards, prospective multi-center validation, transparent reporting, and thoughtful regulatory strategy. With these elements in place, machine learning–driven multi-omics biomarkers have the potential to contribute meaningfully to earlier detection and improved outcomes for patients with small cell lung cancer.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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