Thoracic Cancer

WILEY

REVIEW OPEN ACCESS

PD-L1 Scoring Models for Non-Small Cell Lung Cancer in China: Current Status, AI-Assisted Solutions and Future Perspectives

Ziling Huang[1,2] | Shen Wang[3] | Jiansong Zhou[4] | Haiquan Chen[2,5] | Yuan Li[1,2]

[1]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China | [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China | [3]School of Computer Science, Fudan University, Shanghai, China | [4]Value & Implementation, Global Medical & Scientific Affairs, MSD China, Shanghai, China | [5]Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Correspondence: Haiquan Chen (hqchen1@yahoo.com) | Yuan Li (lumoxuan2009@163.com)

Received: 14 October 2024 | **Revised:** 27 February 2025 | **Accepted:** 5 March 2025

Funding: This work was funded by MSD China. Ziling Huang, Shen Wang, and Yuan Li received grants from the National Key Research and Development Program of China (No. 2021YFF1201001) and The Institution and Governmental Cooperative Project, Shanghai Xuhui District Science and Technology Committee (No. 23XHYD-12).

Keywords: artificial intelligence | immunohistochemistry | non-small cell lung cancer | PD-L1

ABSTRACT

Immunotherapy has revolutionized the diagnosis and treatment model for patients with advanced non-small cell lung cancer (NSCLC). Numerous clinical trials and real-world reports have confirmed that PD-L1 status is a key factor for the successful use of immunotherapy in NSCLC, by predicting clinical outcomes and identifying patients most likely to benefit from this treatment. Therefore, accurate and standardized evaluation of PD-L1 expression is crucial. Currently, PD-L1 testing in China faces several challenges, including a heavy pathologist workload, a shortage of highly trained pathologists plus the inadequate capacity of diagnostic laboratories, confusion around different scoring methods, cut-off values, and indications, and limited concordance between PD-L1 assays. In this review, we summarize the current status and limitations of PD-L1 testing for patients with NSCLC in China and discuss recent progress in artificial intelligence-assisted PD-L1 scoring. Our review aims to support improvements in clinical PD-L1 testing practice and optimization of the prognosis and outcomes of immunotherapy in this patient population.

1 | Introduction

Lung cancer causes significant morbidity and mortality, in China and worldwide [1]. In China, lung cancer is the leading cause of cancer-related mortality, resulting in around one-fourth of all cancer-related deaths, and it remains a major public health problem [2]. Non-small cell lung cancer (NSCLC) is the predominant type of lung cancer, accounting for 80%–85% of all lung cancer cases globally [3]. In recent years, immunotherapy with immune checkpoint inhibitors (ICIs) has revolutionized the diagnosis and treatment model for patients with advanced NSCLC. By binding to the programmed cell death protein 1 (PD-1) receptor on the surface of immune cells such as T cells and B cells, programmed cell death-ligand 1 (PD-L1) (expressed on tumor cells) helps tumors evade immune surveillance and escape destruction by the immune system [4, 5]. Numerous clinical trials and real-world reports have confirmed that ICIs have promising antitumor activity and acceptable toxicity in the treatment of patients with advanced or metastatic NSCLC, and PD-L1

Ziling Huang and Shen Wang contributed equally to this article.

status was confirmed as the ideal biomarker to predict clinical outcomes and identify patients likely to respond to ICI therapy [6]. While not all patients with NSCLC respond to treatment with ICIs, patients with tumors that express high levels of PD-L1 are more likely to respond to ICIs and have better clinical outcomes [7].

Accurate, reproducible, and standardized evaluation of PD-L1 expression in tumor tissues is crucial for the reliable use of PD-L1 as a biomarker to predict treatment outcomes and to select patients for immunotherapy. Currently, PD-L1 testing in China faces several challenges, including heavy pathologist workload, a shortage of highly trained pathologists, inadequate capacity of diagnostic laboratories in certain provinces, confusion around different scoring methods, cut-off values and indications, and limited concordance between PD-L1 assays. In this article, we review the current status and limitations of standard PD-L1 testing for patients with NSCLC in China and discuss recent progress in artificial intelligence-assisted PD-L1 scoring. Our review aims to support improvements in clinical PD-L1 testing practice and optimization of the prognosis and outcomes of immunotherapy in this patient population.

2 | Role and Challenges of Immunotherapy and PD-L1 Testing in NSCLC in China

2.1 | Essential Role and Challenges of Immunotherapy in NSCLC in China

Immunotherapy has become an essential part of NSCLC treatment in China [8]. Since nivolumab was first approved by the Chinese National Medical Products Administration (NMPA) for the treatment of NSCLC in 2018 and followed by pembrolizumab in 2019, several other anti-PD-1/PD-L1 therapies have been approved by the NMPA for the first- or second-line treatment of NSCLC. To date, the NMPA has approved 11 anti-PD-1/PD-L1 monoclonal antibodies (mAbs) for NSCLC, including eight anti-PD-1 antibodies (camrelizumab, nivolumab, pembrolizumab, sintilimab, tislelizumab, toripalimab, penpulimab [AK105], and serplulimab) [8–15] and three anti-PD-L1 antibodies (atezolizumab, durvalumab, and sugemalimab) [8, 9, 11, 16–18] (Table 1). Only atezolizumab and pembrolizumab have been approved for use as monotherapy in the first-line setting in selected patients (Table 1) [9].

Moreover, guidelines from the Chinese Society of Clinical Oncology (CSCO) also recommend immunotherapy for patients with NSCLC (Table 2). However, two recent studies investigating trends in the use of PD-1/PD-L1 inhibitors by oncologists in China showed that platinum-based chemotherapy is the preferred treatment for advanced NSCLC in the first-line setting [19] and less than 60% of Chinese clinicians prescribe PD-1/PD-L1 inhibitors in this setting [20]. This is partly because the objective response rates with ICI monotherapy are typically below 30% for previously treated patients [21], although superior efficacy of ICIs over chemotherapy or placebo has been reported [21–25], and combining ICIs with chemotherapy is associated with objective response rates of up to 50% [24]. In addition, clinicians tend to prefer the use of pembrolizumab monotherapy or in combination with platinum doublet chemotherapy in patients with PD-L1 expression in ≥ 50% of tumor cells [10], and patients with squamous histology are more likely to be prescribed PD-1/PD-L1 inhibitors than those with non-squamous histology in this setting [19]. The high cost of mAbs may also contribute to the lower-than-expected frequency of ICI use in Chinese patients with advanced NSCLC [10]. Therefore, efforts are needed to reinforce an accurate understanding of the rationale and clinical utility of ICIs in NSCLC among Chinese oncologists.

2.2 | Pivotal Role of PD-L1 Expression in Patient Selection

PD-L1 expression is a biomarker for tumor response and survival following treatment with anti-PD-1/PD-L1-based therapies, as shown in the KEYNOTE-407 [26] and KEYNOTE-189 trials [27]. Real-world evidence from China also supports an association between PD-L1 expression and survival following treatment with an ICI and chemotherapy [28, 29]. An artificial intelligence-based model that uses PD-L1 TPS to predict response to ICI treatment was clinically validated in patients with advanced NSCLC [30]. However, methodological variability, as well as the dynamic and heterogeneous nature of PD-L1 expression, have led to uncertainty in test selection and implementation in practice.

2.3 | Challenges in the Implementation of Clinical PD-L1 Testing in NSCLC in China

Following the approval of PD-L1/PD-1 inhibitors by the Chinese NMPA, five companion or complementary diagnostics have been approved (Table 3), all of which are based on the analysis of formalin-fixed paraffin-embedded (FFPE) tumor tissues using immunohistochemistry (IHC) [8]. The *Chinese Expert Consensus on Standards of PD-L1 Immunohistochemistry Testing for Non-small Cell Lung Cancer* published by the Chinese Anticancer Association provides recommendations for the selection of PD-L1 detection reagents and detection platforms [37]. While the 2023 CSCO guidelines recommend PD-L1 expression testing and *EGFR*/*ALK* mutation testing at the initial diagnosis of patients with advanced NSCLC [9], the rate of PD-L1 testing in China is low and varies from hospital to hospital [38]. In addition, the choice of PD-L1 test depends on the therapeutic agent being considered and the stage of NSCLC and can impact the interpretation of PD-L1 expression and subsequent treatment decisions [8]. Additionally, in many regions of China (e.g., Shanghai), PD-L1 testing, such as the 22C3 kit, is not covered by the national medical insurance and this greatly affects the utilization of PD-L1 testing. Regional differences in the utilization of the different PD-L1 kits have been observed between Asia and North America, with higher use of the 28–8 (29% vs. 12%), SP142 (38% vs. 20%), and SP263 (64% vs. 35%) clones in Asia (Figure 1) [39].

According to economic analyses, from the perspective of the Chinese healthcare system, PD-L1 testing is cost-effective in guiding the use of ICIs in patients with advanced NSCLC in the first-line but not in the second-line setting [40, 41]. From a practical perspective, 30%–40% of patients with advanced NSCLC in

TABLE 1 | Immune checkpoint inhibitors approved in China for the treatment of non-small cell lung cancer.

Name	Antibody class	Target	Indications
Atezolizumab [9]	Humanized IgG1 mAb	PD-L1	– As monotherapy for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells or PD-L1 expression in tumor-infiltrating immune cells covering ≥ 10% of the tumor area), without *EGFR* or *ALK* genomic tumor aberrations
Camrelizumab [9]	Humanized IgG4 mAb	PD-1	– In combination with pemetrexed and carboplatin as first-line treatment for patients with unresectable, locally advanced, or metastatic nonsquamous NSCLC, without *EGFR* or *ALK* genomic tumor aberrations
Durvalumab [11, 16, 17]	Humanized IgG1 mAb	PD-L1	– As consolidation treatment for patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy
Nivolumab [10, 11]	Humanized IgG4 mAb	PD-1	– As monotherapy for the second-line treatment of patients with advanced nonsquamous or squamous NSCLC regardless of PD-L1 expression or *EGFR/ALK* status (if not received before) – As monotherapy for the third-line treatment of patients with advanced nonsquamous or squamous NSCLC regardless of PD-L1 expression or *EGFR/ALK* status (if not received before)
Pembrolizumab [9, 10]	Humanized IgG4 mAb	PD-1	– In combination with pemetrexed and platinum chemotherapy as a first-line treatment for patients with metastatic nonsquamous NSCLC, without *EGFR* or *ALK* genomic tumor aberrations – As monotherapy for the first-line treatment of patients with locally advanced or metastatic nonsquamous or squamous NSCLC expressing PD-L1 (TPS ≥ 1%), without *EGFR* or *ALK* genomic tumor aberrations – In combination with carboplatin and paclitaxel as first-line treatment for patients with metastatic squamous NSCLC
Sintilimab [9, 12]	Humanized mAb	PD-1	– In combination with pemetrexed/platinum as first-line treatment for patients with unresectable, locally advanced, or metastatic nonsquamous NSCLC – In combination with platinum/gemcitabine as first-line treatment for patients with unresectable, locally advanced, or metastatic squamous NSCLC
Sugemalimab [18]	Humanized IgG4 mAb	PD-L1	– In combination with pemetrexed and carboplatin as first-line treatment for patients with metastatic nonsquamous NSCLC without *EGFR* or *ALK* tumor mutations – In combination with paclitaxel and carboplatin as first-line treatment for patients with metastatic squamous NSCLC without *EGFR* or *ALK* tumor mutations
Tislelizumab [9]	Humanized IgG4 mAb	PD-1	– In combination with pemetrexed/platinum as first-line treatment for patients with nonsquamous NSCLC – In combination with carboplatin/paclitaxel or nab-paclitaxel as first-line treatment for patients with squamous NSCLC
Toripalimab [13]	Humanized IgG4 mAb	PD-1	– In combination with plus pemetrexed and platinum as first-line treatment for patients with advanced non-squamous NSCLC who do not harbor EGFR mutations or ALK fusions
Penpulimab [AK105] [14]	Fc-engineered IgG1 anti-PD-1 antibody	PD-1	– In combination with paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous, NSCLC
Serplulimab [15]	Humanized IgG4 mAb	PD-1	– In combination with carboplatin and albumin-bound paclitaxel for the first-line treatment of patients with unresectable locally advanced or metastatic squamous non-small cell lung cancer

Abbreviations: mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; TPS, tumor proportion score.

TABLE 2 | Chinese Society of Clinical Oncology recommendations for the use of immunotherapy in non-small cell lung cancer.

Stage	Status/ characteristics	Recommended use	Immunotherapy regimen
Resectable Stage IIIA-B	Following successful resection	Adjuvant therapy	• Atezolizumab monotherapy (PD-L1 TC ≥ 1%) (Level 1 recommendation) • Pembrolizumab monotherapy (Level 2 recommendation)
		Neoadjuvant therapy	• Nivolumab combined with platinum-based therapy (Level 1 recommendation)
	N_2 disease and unable to undergo radical resection	Consolidation therapy following chemoradiotherapy	• Durvalumab or sugemalimab (Level 1 recommendation)
Unresectable Stage IIIA-C	ECOG PS 0–1	Consolidation therapy following chemoradiotherapy	• Durvalumab or sugemalimab (Level 1 recommendation)
	ECOG PS 2	Same as recommendations for Stage IV without driver mutations (Level 2 recommendation)	
Stage IV non-squamous NSCLC without driver mutations	First-line, ECOG PS 0–1	Systemic treatment	• Atezolizumab monotherapy (PD-L1 TC score ≥ 50% or IC ≥ 10%) (Level 1 recommendation) • Pembrolizumab (PD-L1 TPS ≥ 50% or TPS 1%–49% [2A]) (Level 1 recommendation) • Pemetrexed plus platinum chemotherapy combined with pembrolizumab, camrelizumab, sintilimab, tislelizumab, atezolizumab, sugemalimab, or toripalimab (Level 1 recommendation) • Paclitaxel plus carboplatin + bevacizumab + atezolizumab (Level 2 recommendation) • Albumin bound paclitaxel plus carboplatin + bevacizumab + atezolizumab (Level 2 recommendation) • Two cycles of pemetrexed plus platinum-based chemotherapy + nivolumab + ipilimumab (Level 3 recommendation)
	Second-line, ECOG PS 0–2	Systemic treatment	• Nivolumab or tislelizumab, if not used in first line (Level 1 recommendation) • Pembrolizumab (PD-L1 TPS ≥ 1%) or atezolizumab (Level 2 recommendation)
	Third-line, ECOG PS 0–2	Systemic treatment	• Nivolumab (if not already used) (Level 1 recommendation)

Abbreviations: ECOG PS, Eastern Co-operative Oncology Group Performance Status; IC, immune cell; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; TC: tumor cell; TPS: tumor proportion score.

China only have cytology specimens available for analysis [42], suggesting a potential limitation in obtaining adequate tissue samples for PD-L1 testing. A study also found that long-term storage of paraffin-embedded tissues leads to antigen loss, but this can be delayed by refrigerated storage at −80°C [43]. There are also differences in the genomic profiles of Chinese patients with NSCLC versus their Western counterparts, with a higher prevalence of EGFR mutations and ALK rearrangements and a lower frequency of KRAS mutations [44].

3 | Complex PD-L1 Testing Requires Experienced Pathologists

3.1 | Complexity of Domestic PD-L1 Testing

Companion diagnostics are mandatory tests that must be performed before treatment is initiated, and complementary tests aid the therapeutic decision process but are not required when prescribing the corresponding ICI [45]. As shown in Table 3, the

TABLE 3 | NMPA-approved assays for PD-L1 testing in non-small cell lung cancer in China.

	PD-L1 assays [7–9, 31–36]				
Clone	**22C3[a]**	**28–8[a]**	**SP142[a]**	**SP263[a]**	**E1L3N**
Platform	AutoStainer Link 48		Ventana Benmark Ultra		Laboratory-developed platform
Scoring system	TPS	TPS	TC, IC	TC	TPS
Drug	Pembrolizumab Camrelizumab Sintilimab	Nivolumab	Atezolizumab	Durvalumab	Pembrolizumab
Companion diagnostic	✓	✓	✓	✓	✓
Complementary diagnostic			✓		

Abbreviations: IC, immune cell; NMPA, National Medical Products Administration; PD-L1, programmed death-ligand 1; TC, tumor cell; TPS, tumor proportion score.
[a]Approved by both the US FDA and China NMPA.

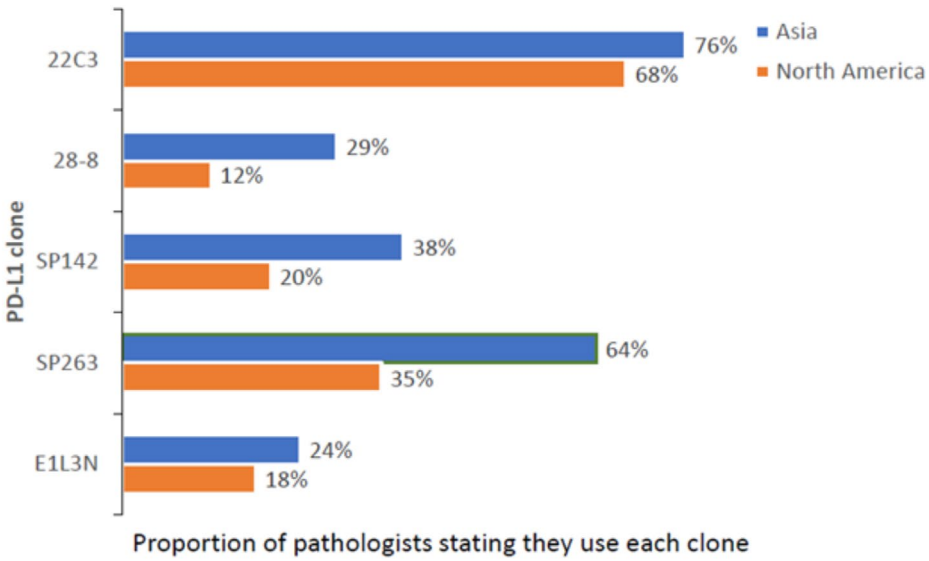

FIGURE 1 | Use of PD-L1 clones in Asia and North America based on a global survey of pathologists. The figure shows the self-reported use of different PD-L1 clones for PD-L1 testing among pathologists in Asia and North America. PD-L1, programmed death ligand 1. Drawn from data published by Mino-Kenudson et al. [39].

currently available PD-L1 assays differ in their antibody clones, platforms, scoring algorithms, and cutoff values for defining PD-L1 positivity. Therefore, pathologists must familiarize themselves with the specifications of each PD-L1 assay to correctly interpret PD-L1 testing results.

In terms of scoring algorithms, various metrics are used to estimate PD-L1 expression in NSCLC. Tumor proportion score (TPS), the scoring metric used for the 22C3 and 28–8 assays (used for pembrolizumab, camrelizumab, sintilimab, and nivolumab) represents the percentage of viable tumor cells showing partial or complete membrane staining for PD-L1 at any intensity [31, 46]. For the 22C3 assay, a TPS score of ≥ 1% indicates PD-L1 expression, and a TPS score of ≥ 50% indicates high PD-L1 expression [32, 46–49]. In contrast, for the 28–8 assay, TPS ≥ 25% is used to determine PD-L1 positivity. Tumor cell (TC) score represents the percentage of tumor cells with positive staining in the total tumor area and is the scoring method used for the SP263 and SP142 assays (used for atezolizumab and durvalumab) [31, 46]. PD-L1 positivity using TC score is defined as TC ≥ 50% [46]. The immunocyte (IC) score is used as a scoring method for the SP142 assay to report the percentage of immune cells with positive staining in the total tumor area [31, 46]. There are no widely accepted cutoff values for determining PD-L1 expression on immune cells. However, NSCLC samples with IC ≥ 10% are typically considered PD-L1-positive [46].

3.2 | High Demand for Experienced Pathologists

PD-L1 scoring accuracy and repeatability depend on expert experience. Manual assessment of IHC is the current gold standard, and inter-observer variability is inevitable [50]. However, expert pathologists have shown higher concordance in PD-L1

scoring in NSCLC than less experienced pathologists [51], suggesting that specialized training is needed to maintain consistency and quality of interpretation between pathologists [46]. Indeed, studies have shown that obtaining formal training on TPS can increase concordance in PD-L1 testing in NSCLC [52, 53]. Nonetheless, highly experienced pathologists are scarce, and providing specialized training to pathologists is not always feasible. While implementing continuing education and training could improve pathologists' ability to interpret PD-L1 scores, the complexity of the Chinese healthcare system (e.g., from primary hospitals to tertiary hospitals) [54], the high costs of training [55], and the heavy workload of Chinese pathologists [56, 57] make it challenging to provide training to all pathologists.

4 | Clinical PD-L1 Assay Limitations

4.1 | Limitations in the Implementation of Clinical PD-L1 Testing

PD-L1 assays are routinely used in clinical practice to determine PD-L1 expression in patients with NSCLC. However, differences in assay antibodies, platforms, scoring algorithms, and cutoff values can lead to variability in PD-L1 expression results and may influence patient eligibility for immunotherapy [58–60]. Expert panel members of the College of American Pathologists (CAP) concluded that the balance of effects (benefits and harms) did not favor either companion diagnostic (CDx) assays or laboratory-developed tests (LDTs) [61]. However, to date, the available PD-L1 IHC assays have not been clinically validated for cross-utilization [58].

There is also difficulty in determining what constitutes an optimal specimen for testing in patients with advanced NSCLC, in terms of testing of the primary tumor and/or metastatic sites, using small biopsy samples (core biopsies, cytology specimens, and endobronchial biopsies) and/or resection specimens. TPS scores obtained from the primary tumor and synchronous metastatic lesions are discordant versus resected specimens approximately 20% to 30% of the time, at both the 1% and 50% cutoffs [62–65]. Furthermore, intratumoral heterogeneity of PD-L1 expression is common in resection specimens, leading to different results obtained from small biopsy samples [27, 66, 67].

Finally, a lack of uniform guidelines for scoring PD-L1 expression across different laboratories and institutions also makes it difficult to compare PD-L1 test results and may lead to inconsistent treatment decisions. Therefore, efforts are needed to harmonize testing methodologies in China and internationally.

4.2 | Manual Inspection Is Time Consuming and Labor Intensive

Standard PD-L1 scoring methods require pathologists to manually examine stained tissue samples under a microscope, which is time-consuming and labor intensive [68]. Because of the large population (1.37 billion) of China and the increasing disease incidence and detection rate for lung cancer, the workload of pathologists in China has become extremely heavy, and the requirements for test quality, turnaround time, and reporting cycle are increasingly high [57].

4.3 | Multiple Metrics to Improve Predictive Performance

Current PD-L1 assays rely solely on PD-L1 expression as a predictive biomarker and may overlook other inhibitory receptors and ligands involved in immune regulation [7–9, 31–35]. Combining PD-L1 expression with additional biomarkers, such as tumor mutational burden (TMB), CD8+ T cell infiltration, and HLA class I expression, may provide a more comprehensive understanding of the immunological status of a tumor. However, integrating multiple biomarkers further increases the time required for manual scoring of IHC-stained tissue slides.

5 | Strategies for Optimizing Testing Practices

Several efforts have been made to overcome the limitations of standard PD-L1 scoring methods. Guidelines and consensus statements may help to standardize the assay process, including antibody/platform selection, scoring methods, and cutoff values, to ensure consistent and accurate quantification of PD-L1 and other biomarkers [69, 70]. In this regard, the recent publication of a Chinese expert consensus on PD-L1 testing for NSCLC [37, 71] or solid tumors [72] provides an initial step toward standardized testing and reporting. Additionally, the implementation of training programs, guidelines, and quality control initiatives can help minimize variability and ensure consistent interpretation of PD-L1 testing results. Several international projects have also been launched to standardize IHC-based PD-L1 assays. The most prominent is the Blueprint PD-L1 Immunohistochemistry Comparability Project, led by the International Association for the Study of Lung Cancer [73, 74].

Moreover, sampling multiple tumor regions and longitudinal retesting could help overcome the challenge of heterogeneity in PD-L1 expression in NSCLC [75]. Nonetheless, this may be technically challenging and time-consuming, further increasing the workload of Chinese pathologists. In addition, extensive pathologist training and the use of standard protocols and thresholds have been shown to increase inter-observer concordance in PD-L1 scoring. Digital image analysis software and ongoing quality assurance programs are critical for ensuring consistent and accurate interpretation of PD-L1 status. Online training tools [53] and digital pathology platforms [76, 77] have been developed to assist pathologists in PD-L1 interpretation and improve the accuracy and reproducibility of PD-L1 scoring. Automated scoring methods may also accelerate PD-L1 testing and alleviate the burden on pathologists [76, 78]. The increasing use of digital pathology and AI in routine practice provides an opportunity to leverage these tools to improve the clinical value of PD-L1 expression in NSCLC.

6 | Clinical Value of AI-Assisted PD-L1 Scoring Methods

6.1 | AI Models Optimize PD-L1 Clinical Assay Implementation

AI models can perform tasks that require human intelligence, including visual perception, decision making, communication, learning, and problem solving [79]. The improvement of

automated PD-L1 scoring using AI-based models is overcoming some of the limitations of manual scoring by pathologists using standard PD-L1 scoring methods and increasing the efficiency of pathology workflows and scoring throughput. Several studies have demonstrated the feasibility of using AI models to automate digital image analysis and help pathologists analyze PD-L1 expression and predict response to ICIs. We summarize the performance of these models in Table 4. Overall, the results of these studies are encouraging, demonstrating that automated PD-L1 expression analysis using AI models provides high specificity and accuracy in determining PD-L1 expression on tumor cells comparable to manual scoring by trained pathologists and can improve the efficiency of PD-L1 scoring [80–87].

6.1.1 | AI Model Scoring Exploration

Cheng et al. [82] developed a deep learning model to analyze PD-L1 expression in IHC-stained tissues from 1288 patients with lung cancer. Tissues were stained for PD-L1 using both the 22C3 and SP263 assays. The AI model showed high performance in scoring PD-L1 expression in tissues stained with 22C3, especially at TPS ≥ 1%. High accuracy and specificity were also achieved when the AI model was used to determine PD-L1 expression in tissues stained with SP263. The PD-L1 scoring results with AI were consistent with those obtained manually by a pathologist [82]. These results suggest that AI models could help automate PD-L1 scoring in IHC-stained NSCLC tissues.

Aitrox (a new AI segmentation model) [83] and AIM-PD-L1-NSCLC (a scanner- and antibody-agnostic machine learning model) [84] have also been tested as AI-assisted PD-L1 scoring systems for NSCLC. Aitrox was trained on 54 whole slide images (WSIs) [83], and AIM-PD-L1-NSCLC was trained to identify PD-L1-positive cells in digitized WSIs of NSCLC tissue samples collected at various institutions [84]. When used to score PD-L1 expression in IHC-stained NSCLC images, Aitrox provided PD-L1 scores similar to those obtained by experienced pathologists [83]. In addition, Aitrox performed better than inexperienced pathologists in determining PD-L1 scores [83]. AIM-PD-L1-NSCLC provided PD-L1 scores that were highly concordant with those obtained by board-certified pathologists, regardless of the PD-L1 antibody clone used to stain the tissues [84].

6.1.2 | AI Models for Efficacy Prediction and Biomarker Screening

AI models have also been tested for their ability to predict response to anti-PD-1/PD-L1 therapies. Lunit SCOPE PD-L1 is an AI model trained on 393,565 tumor cells manually annotated by a pathologist for PD-L1 expression in 802 WSIs stained using the 22C3 assay [88]. The model accurately predicted PD-L1 expression, with an AUC value of 0.889. High concordance rates in TPS between the AI model and the pathologist were observed for high TPS values (85.7% for PD-L1 ≥ 50% and 89.3% for PD-L1 1%–49%). When stratified into two subgroups based on AI-predicted TPS (≥ 1% vs. < 1%), there was a significant difference in median progression-free survival between the two patient groups (2.8 vs. 1.7 months; hazard ratio [HR]: 0.52; 95% CI: 0.38–0.71; $p < 0.001$) [88]. Although both manual and AI-powered prediction of PD-L1 scores can predict response to ICIs, studies suggest that patient stratification based on AI-derived PD-L1 scores can result in improved associations with survival after treatment with ICIs [79, 88].

AI has also been used to predict response to ICIs by combining PD-L1 with other biomarkers. Althammer et al. [78] used AI to score digital images for PD-L1+ and CD8+ cell densities and developed a CD8xPD-L1 signature to mark NSCLC samples with high PD-L1+/CD8+ cell densities. They found that median overall survival after treatment with durvalumab was longer for CD8xPD-L1 signature-positive patients than for signature-negative patients (21.0 vs. 7.8 months; $p = 0.00002$) [78]. These findings suggest that the use of AI to identify NSCLC samples with high PD-L1+/CD8+ cell densities could aid pathologists in selecting patients who are likely to respond to durvalumab therapy.

6.2 | Limitations and Challenges of AI-Assisted PD-L1 Scoring Methods

Although AI has shown promise in increasing the accuracy of PD-L1 scoring in NSCLC, the technology is relatively new, and several technological challenges must be addressed (Figure 2). Firstly, almost all published studies evaluating the feasibility and performance of AI-assisted PD-L1 scoring methods are retrospective (Table 4). Large prospective studies are needed to validate the ability of AI models to accurately quantify PD-L1 expression in digitized NSCLC tissue images and predict response to anti-PD-1/PD-L1 therapies. Secondly, although AI models can improve objectivity and reduce certain human-specific biases [91], they can also introduce other types of bias. For example, confounding effects, such as those introduced during the preparation of sample slides, as well as imbalances in the training datasets, can introduce biases in AI-assisted decisions [92]. Underfitting and overfitting are two common issues in training and evaluating AI models that have a significant impact on bias and variance, especially due to a lack of high-quality, extensively labeled pathology images. Underfitting occurs when a model is too simple to capture the underlying patterns in the data, leading to high training and testing errors due to high bias and low variance [93]. On the other hand, overfitting occurs when a model is excessively complex, capturing noise in the training data and resulting in low training error but high testing error due to low bias and high variance. Most published studies evaluating the use of AI to predict PD-L1 expression or response to immunotherapy are small, and AI training is particularly prone to overfitting when using small datasets. Image segmentation algorithms using AI may be helpful in reducing human-specific biases and other biases (Huang et al. in preparation). Ethical and legal concerns of AI should also be taken into consideration. Many uncertainties remain regarding the integration and management of patient data when AI systems are used to reach a diagnosis or make treatment decisions [94, 95]. Key ethical issues to consider when using AI to score PD-L1 expression or identify patients who may benefit from treatment with ICIs

TABLE 4 | Performance of AI models in predicting PD-L1 expression and treatment response in non-small cell lung cancer.

Study	Design	Samples	Task	Metric, cutoff	AUC	ICC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Association with ICI response
Naso et al. 2021 [80]	Retrospective	IHC-stained tissues	PD-L1 scoring	TPS, ≥1%	NR	0.80 (0.71–0.88)	NR	95	84	NR
Pan et al. 2021 [81]	Retrospective	IHC-stained tissues	PD-L1 scoring	TPS, ≥1%	NR	SP263: 0.873 (0.835–0.903) 22C3: 0.737 (0.641–0.810)	NR	NR	NR	NR
Cheng et al. 2022 [82]	Retrospective	IHC-stained tissues	PD-L1 scoring	TPS, ≥1%	NR	NR	96.4	94.07	95.02	NR
Huang et al. 2022 [83]	Retrospective	IHC-stained tissues	PD-L1 scoring	TPS	NR	NR	TPS < 1%: 85.29 TPS 1%–49%: 77.97 TPS > 50: 72.73	NR	NR	NR
Griffin et al. 2022 [84]	Retrospective	IHC-stained tissues	PD-L1 scoring	TPS	NR	0.93 (0.90–0.94)		NR	NR	NR
Wu et al. 2022 [85]	Retrospective	IHC-stained tissues	PD-L1 scoring	TPS	NR	0.866 (0.787–0.922)	0.9326	NR	0.9641	NR
Lim et al. 2022 [86]	Retrospective	312 PET/CT scans (189 adenocarcinomas, 123 squamous cell carcinomas)	Prediction of PD-L1 expression	TPS, ≥ 50%	0.712[a]	NR	NR	75.3	58.2	NR
Zhao et al. 2023 [87]	Retrospective	334 PET/CT scans	Prediction of PD-L1 expression	TPS, ≥1%	0.761[a]	NR	70.30	68.52	72.34	NR
Kim et al. 2021 [88]	Retrospective	IHC-stained tissues	Prediction of PD-L1 expression and response to ICIs	TPS, ≥1%	0.889[b]	NR	NR	NR	NR	mPFS in TPS ≥1% versus <1%: 2.8 versus 1.7 months (HR: 0.52 [95% CI]: 0.38–0.71; $p < 0.001$)

(Continues)

TABLE 4 | (Continued)

Study	Design	Samples	Task	Metric, cutoff	AUC	ICC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Association with ICI response
Baxi et al. 2022 [79]	Retrospective	IHC-stained tissues	Prediction of PD-L1 expression and response to ICIs	TC, ≥ 1% or ≥ 5%	0.602[b]	NR	NR	NR	NR	ORR in TC < 1% versus ≥ 1%: 5.3 versus 21.1 (OR: 5.08 [95% CI: 0.65–39.55]) ORR in TC < 5% versus ≥ 5%: 9.5 versus 25.8 (OR: 3.53 [95% CI: 0.79–15.67])
Althammer et al. [78]	Prospective	IHC-stained tissues	Scoring for PD-L1+/CD8+ cell densities, prediction of response to ICIs	NR	NR	NR	NR	NR	NR	mOS in CD8xPD-L1 signature-positive versus signature-negative: 21.0 versus 7.8 months ($p = 0.00002$)
Vaidya et al. 2020 [89]	Retrospective	Pretreatment CT scans	Predict risk of hyperprogression	NR	0.96[b]	NR	NR	NR	NR	HR for OS: 2.66 [95% CI: 1.27–5.55]; $p = 0.009$
Mu et al. 2021 [90]	Retrospective	697 PET/CT scans	Prediction of PD-L1 expression and response to ICIs	TPS, ≥ 1%	0.84[b]	NR	78.45	77.43	81.48	HR for PFS in DLS ≥ 0.55 versus < 0.55: 0.41 (95% CI: 0.25–0.67), $p = 0.001$ HR for OS in DLS ≥ 0.55 versus < 0.55: 0.48 (95% CI: 0.25–0.91), $p = 0.024$

Abbreviations: AI, artificial intelligence; AUC, area under the receiver operating characteristic curves; CI, confidence interval; DLS, deeply learned score; HR, hazard ratio; ICC, intraclass correlation coefficient; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; OR, odds ratio; ORR, objective response rate; PD-L1, programmed death-ligand 1; PET/CT, positron emission tomography/computed tomography; TC, tumor cell; TPS, tumor proportion score.

[a]For predicting PD-L1 expression.

[b]For predicting objective response.

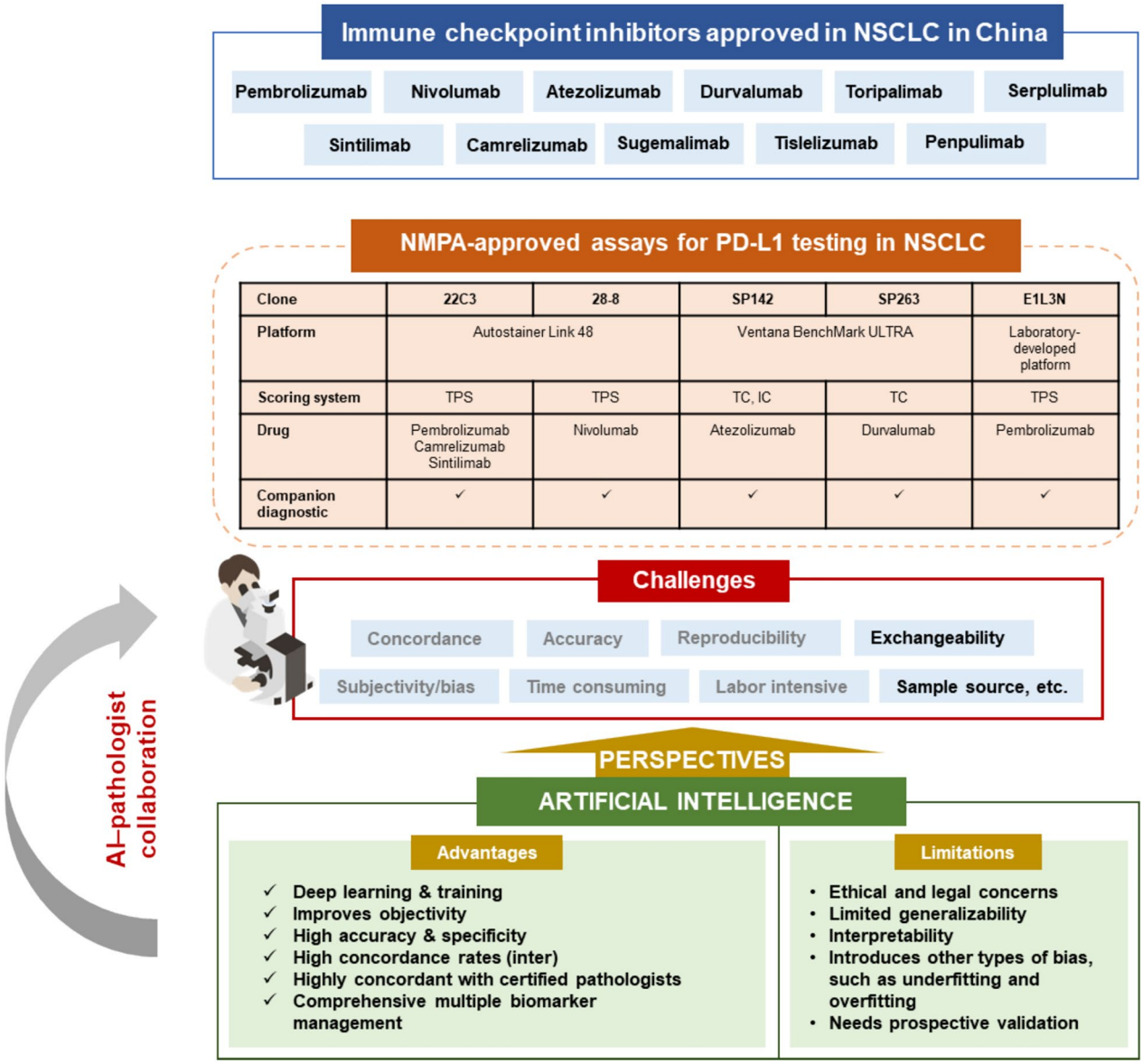

FIGURE 2 | Summary of advantages and challenges for using artificial intelligence models to assist PD-L1 scoring illustration: DataBase Center for Life Science (DBCLS), CC BY 4.0 (https://creativecommons.org/licenses/by/4.0), via Wikimedia Commons. IC, immune cell; NMPA, China National Medical Products Administration; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TC, tumor cell; TPS, tumor proportion score.

include privacy, choice, equity, trust, and assigning responsibility if errors are made [95]. Currently, risk regulation is increasingly used to govern AI systems, focusing on managing the risks associated with AI rather than outright banning its use. Determining who has responsibility when AI makes a mistake involves a multifaceted approach including updating legal frameworks, implementing hybrid liability regimes, and ensuring transparency and accountability. Ongoing efforts by the EU and other international bodies are crucial steps toward addressing these challenges and ensuring that AI technologies are used responsibly and ethically [96, 97]. Laws, regulations, and robust public governance mechanisms and ethical frameworks are required to ensure the ethical use of AI models and protect patient privacy. These are reasons for insufficient high-quality massively labeled training samples for AI pathology models.

The limited generalizability across patient populations due to small sample sizes, data imbalances, and heterogeneity between datasets are further barriers to the clinical implementation of AI-assisted diagnostic methods [79, 94]. In most published studies, AI models were trained using relatively small datasets; thus, the performance of AI-assisted PD-L1 scoring methods in underrepresented populations or in patients with rare tumor subtypes remains unknown [94]. Extensive training on large datasets comprising images from diverse patient populations and samples representing different histological and molecular subtypes and clinical stages is needed to increase the generalizability of AI-assisted PD-L1 scoring models. In addition, AI models have shown limited robustness in certain settings. Validation studies have confirmed that AI models perform as well as or better than pathologists in most settings [82, 85]; however, their performance

is poor when used to analyze images with low PD-L1 expression (52.4% for images with TPS < 1%) [88], especially those with large regions of false-positive cells [83]. Therefore, AI algorithms should be optimized, extensively validated, and reviewed before their implementation, and their performance should be verified to ensure that they are safe, efficacious, and reliable.

Interpretability and access to technology should also be improved to fully realize the potential of AI to support treatment decisions for patients with NSCLC. The limited interpretability of AI, also referred to as the "black box", is a critical issue that hinders the widespread clinical adoption of AI-assisted systems [94]. Training programs on AI are warranted to ensure that pathologists know how to use AI models and interpret AI-assisted PD-L1 testing results.

Access to digital pathology in China is currently limited and faces several challenges. Digital pathology was initiated relatively late in China and has progressed more slowly compared to other countries. There is currently no comprehensive implementation of complete digital pathology (CDP) in China [98]. Despite this, the development of digital pathology has been accelerated through advances in technologies such as the internet, big data, and AI. In addition, the Chinese healthcare industry is leveraging cloud and mobile computing to enable better collaboration and access to medical information. Government support and assistance from international companies are also playing a role in the development of digital pathology. Indeed, in the present day, China is a key international contributor to the development of digital pathology, particularly in lung cancer. For example, the integration of whole-slide imaging technology with AI algorithms is particularly significant in the context of lung cancer, where it enhances the accuracy of classification and prediction. However, most research in China is conducted independently, highlighting the need for stronger academic collaboration and data sharing between nations [99]. There are also significant challenges related to cognition, classification, and quality that need to be addressed. The future development of digital pathology in China will likely involve the integration of AI and big data to enhance diagnostic capabilities and personalized medicine. This will require addressing current barriers and leveraging international experiences and technologies [98, 99].

Last but not least, AI models require extensive validation before clinical implementation in China and have their own challenges. For example, the cost and accessibility of AI technology may limit its widespread implementation in clinical practice [100]. AI in pathology in China is currently in the research stage [101], and investing in AI-related software and hardware can be expensive. Efficient and high-quality scanners are needed to ensure that the implementation of AI will improve work efficiency. However, the degree of automation of instruments currently available in most pathology departments in China is not high [56].

6.3 | AI–Pathologist Collaboration and Enhancement

Although AI has show promise in increasing the accuracy and reproducibility of PD-L1 scoring in NSCLC, AI models are unlikely to replace pathologists in PD-L1 scoring [102, 103]. Instead, pathologists will be aided by AI models to accurately and quickly analyze large datasets of digitized tissue images to determine PD-L1 expression and make treatment decisions. In this workflow, pathologists play a key role in the operation and interpretation of the technology. However, some aspects of their work may change because tedious, time-consuming, and manual tasks can be automated using AI.

In this collaborative model, pathologists play a crucial role in training the AI algorithm using manually annotated training images, as well as in performing quality control by assessing the accuracy and reproducibility of results [102, 103]. Pathologists also play a critical role in the validation, implementation, and interpretation of AI-assisted systems, ensuring their accuracy and reliability in clinical practice [104]. AI models can also be used to confirm PD-L1 testing results obtained through manual scoring by a pathologist. The College of American Pathologists has developed guidelines for the validation of WSI systems for diagnostic use [105], according to which pathologists play a crucial role in validating and verifying the performance of these systems to ensure their suitability for clinical use [105].

Training and education are essential to enable pathologists to use digital pathology systems effectively to increase their productivity, reduce diagnostic turnaround times, increase the clinical value of PD-L1, and reduce diagnostic errors. The Royal College of Pathologists has provided guidance for digital pathology implementation, which includes recommendations for training and validation [106]. Pathologists need to be trained in the use of digital pathology systems, including image acquisition, interpretation, and analysis [106]. Pathologists also play a role in training and mentoring other healthcare professionals in the use of digital pathology technology [106]. Although a nationwide telepathology consultation and quality control program was implemented in China in 2014 [107], Chinese guidelines on the implementation of AI-assisted PD-L1 scoring models and other digital pathology systems are currently lacking.

In summary, AI, along with automation, has the potential to improve workflow efficiency and address pathologist capacity limitations by aiding in diagnostic tasks and automating routine processes. For instance, AI-based image analysis can help mitigate staffing shortages by improving diagnostic efficiency and standardizing evaluations [108, 109]. However, education and experience with AI are needed to support its implementation across allied health professions [110]. We believe that training and partnerships with academic institutions can help prepare the workforce for AI integration.

7 | Prospects

Accurate evaluation of PD-L1 expression is critical for identifying patients with NSCLC who are most likely to benefit from immunotherapy. Conventional PD-L1 testing is limited by subjectivity, variability, and a lack of standardization. Recent advances in AI have led to the emergence of numerous AI-assisted PD-L1 scoring methods, which could help overcome some of the limitations of standard PD-L1 testing methods. AI-based models have shown promise in automating PD-L1 scoring while

providing high specificity and accuracy. In addition, although PD-L1 expression is an important biomarker for immunotherapy response, ongoing exploration and development of additional predictive biomarkers are necessary to obtain a more comprehensive understanding of tumor-immune interactions and improve patient selection for immunotherapy. PD-L1 expression can be dynamic and heterogeneous within tumors, leading to sampling bias and potential misclassification [75]. Various studies have explored predictive biomarkers beyond PD-1/PD-L1 receptors to enhance the prediction of immunotherapy response in NSCLC [111–114]. Integrating additional biomarkers, such as TMB, gene mutations, microsatellite instability, HLA expression, and IFNγ level with PD-L1 expression may enhance the prediction of immunotherapy response.

It is important to note that the currently available AI tools for pathology have flaws and limitations. Ongoing research on improving current AI models, harmonizing testing methodology, minimizing technical and interpretation variability, correlating results with clinical outcomes, and addressing ethical concerns is essential to optimize the use of ICIs in the treatment of NSCLC in China. Further research is necessary to refine and validate AI-powered PD-L1 scoring methods to ensure their safe, effective, and reliable use in clinical practice. Generative AI tools are also gaining popularity, and future studies are needed to explore their potential use in supporting clinical decisions for patients with NSCLC. Only through such efforts can the promise of precision immunotherapy based on PD-L1 status be fully realized for Chinese patients with advanced NSCLC.

Author Contributions

Conceptualization: Ziling Huang, Shen Wang, Jiansong Zhou, Haiquan Chen, and Yuan Li. *Writing – Original Draft Preparation*: Ziling Huang, Shen Wang, and Jiansong Zhou. *Writing – Review and Editing*: Ziling Huang, Shen Wang, Jiansong Zhou, Haiquan Chen, and Yuan Li. *Supervision*: Haiquan Chen and Yuan Li. All authors read and approved the final version of the manuscript.

Acknowledgments

Editorial support for this review article was provided by Jake Burrell, PhD (Rude Health Consulting). This assistance was funded by MSD China.

Conflicts of Interest

Jiansong Zhou reported that he was an MSD China employee at the time of writing. Other authors have no conflicts of interest to declare.

Data Availability Statement

All data reported in this review were sourced from the cited references.

References

1. H. Sun, H. Zhang, H. Cai, et al., "Burden of Lung Cancer in China, 1990–2019: Findings From the Global Burden of Disease Study 2019," *Cancer Control* 30 (2023): 10732748231198749, https://doi.org/10.1177/10732748231198749.

2. M. Cao and W. Chen, "Epidemiology of Lung Cancer in China," *Thoracic Cancer* 10 (2019): 3–7, https://doi.org/10.1111/1759-7714.12916.

3. D. Planchard, S. Popat, K. Kerr, et al., "Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up," *Annals of Oncology* 29 (2018): iv192–iv237, https://doi.org/10.1093/annonc/mdy275.

4. P. Dong, Y. Xiong, J. Yue, S. J. B. Hanley, and H. Watari, "Tumor-Intrinsic PD-L1 Signaling in Cancer Initiation, Development and Treatment: Beyond Immune Evasion," *Frontiers in Oncology* 8 (2018): 386, https://doi.org/10.3389/fonc.2018.00386.

5. M. Yarchoan, L. A. Albacker, A. C. Hopkins, et al., "PD-L1 Expression and Tumor Mutational Burden Are Independent Biomarkers in Most Cancers," *JCI Insight* 4, no. 6 (2019): 20190321, https://doi.org/10.1172/jci.insight.126908.

6. X. Liu, C. Y. Guo, F. F. Tou, et al., "Association of PD-L1 Expression Status With the Efficacy of PD-1/PD-L1 Inhibitors and Overall Survival in Solid Tumours: A Systematic Review and Meta-Analysis," *International Journal of Cancer* 147, no. 1 (2020): 116–127, https://doi.org/10.1002/ijc.32744.

7. S. Lantuejoul, M. Sound-Tsao, W. A. Cooper, et al., "PD-L1 Testing for Lung Cancer in 2019: Perspective From the IASLC Pathology Committee," *Journal of Thoracic Oncology* 15, no. 4 (2020): 499–519, https://doi.org/10.1016/j.jtho.2019.12.107.

8. Chinese Association for Clinical Oncologists and Medical Oncology Branch of Chinese International Exchange and Promotion Association for Medical and Healthcare, "Clinical Practice Guideline for Stage IV Primary Lung Cancer in China (2023 Edition)," *Zhonghua Zhong Liu Za Zhi* 45 (2023): 1–30, https://doi.org/10.3760/cma.j.cn112152-20221009-00687.

9. A. Xiong, J. Wang, and C. Zhou, "Immunotherapy in the First-Line Treatment of NSCLC: Current Status and Future Directions in China," *Frontiers in Oncology* 11 (2021): 757993, https://doi.org/10.3389/fonc.2021.757993.

10. S. Gao, N. Li, S. Wang, et al., "Lung Cancer in People's Republic of China," *Journal of Thoracic Oncology* 15 (2020): 1567–1576, https://doi.org/10.1016/j.jtho.2020.04.028.

11. Y. Jin, H. Li, P. Zhang, M. Yu, H. Zhang, and X. Li, "The Regulatory Approvals of Immune Checkpoint Inhibitors in China and the United States: A Cross-National Comparison Study," *International Journal of Cancer* 152, no. 11 (2023): 2351–2361, https://doi.org/10.1002/ijc.34427.

12. L. Zhang, W. Mai, W. Jiang, and Q. Geng, "Sintilimab: A Promising Anti-Tumor PD-1 Antibody," *Frontiers in Oncology* 10 (2020): 594558, https://doi.org/10.3389/fonc.2020.594558.

13. Z. Wang, L. Wu, B. Li, et al., "Toripalimab Plus Chemotherapy for Patients With Treatment-Naive Advanced Non-Small-Cell Lung Cancer: A Multicenter Randomized Phase III Trial (CHOICE-01)," *Journal of Clinical Oncology* 41, no. 3 (2023): 651–663, https://doi.org/10.1200/jco.22.00727.

14. S. Dhillon, "Penpulimab: First Approval," *Drugs* 81 (2021): 2159–2166, https://doi.org/10.1007/s40265-021-01640-9.

15. Y. Cheng, L. Han, L. Wu, et al., "Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients With Extensive-Stage Small Cell Lung Cancer: The ASTRUM-005 Randomized Clinical Trial," *JAMA* 328 (2022): 1223–1232, https://doi.org/10.1001/jama.2022.16464.

16. L. Guo, R. Wei, Y. Lin, and H. F. Kwok, "Clinical and Recent Patents Applications of PD-1/PD-L1 Targeting Immunotherapy in Cancer Treatment-Current Progress, Strategy, and Future Perspective," *Frontiers in Immunology* 11 (2020): 1508, https://doi.org/10.3389/fimmu.2020.01508.

17. Y. Cheng, Q. Zhou, B. Han, et al., "NEPTUNE China Cohort: First-Line Durvalumab Plus Tremelimumab in Chinese Patients With Metastatic Non-Small-Cell Lung Cancer," *Lung Cancer* 178 (2023): 87–95, https://doi.org/10.1016/j.lungcan.2023.01.013.

18. S. Dhillon and S. Duggan, "Sugemalimab: First Approval," *Drugs* 82 (2022): 593–599, https://doi.org/10.1007/s40265-022-01693-4.

19. L. Durbin, B. Murali, S. Li, et al., "Treatment Patterns in Non-Small-Cell Lung Cancer in China: Results From the CancerMPact Survey 2020," *Cancer Treatment and Research Communications* 29 (2021): 100462, https://doi.org/10.1016/j.ctarc.2021.100462.

20. B. Zhang, Y. Song, Y. Fu, B. Zhu, B. Wang, and J. Wang, "Current Status of the Clinical Use of PD-1/PD-L1 Inhibitors: A Questionnaire Survey of Oncologists in China," *BMC Cancer* 20, no. 1 (2020): 86, https://doi.org/10.1186/s12885-020-6583-3.

21. S. J. Antonia, A. Villegas, D. Daniel, et al., "Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer," *New England Journal of Medicine* 377, no. 20 (2017): 1919–1929, https://doi.org/10.1056/NEJMoa1709937.

22. Y. L. Wu, L. Zhang, Y. Fan, et al., "Randomized Clinical Trial of Pembrolizumab vs Chemotherapy for Previously Untreated Chinese Patients With PD-L1-Positive Locally Advanced or Metastatic Non-Small-Cell Lung Cancer: KEYNOTE-042 China Study," *International Journal of Cancer* 148, no. 9 (2021): 2313–2320, https://doi.org/10.1002/ijc.33399.

23. M. Reck, D. Rodriguez-Abreu, A. G. Robinson, et al., "Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater," *Journal of Clinical Oncology* 37, no. 7 (2019): 537–546, https://doi.org/10.1200/JCO.18.00149.

24. L. Gandhi, D. Rodriguez-Abreu, S. Gadgeel, et al., "Pembrolizumab Plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer," *New England Journal of Medicine* 378 (2018): 2078–2092, https://doi.org/10.1056/NEJMoa1801005.

25. R. S. Herbst, G. Giaccone, F. de Marinis, et al., "Atezolizumab for First-Line Treatment of PD-L1-Selected Patients With NSCLC," *New England Journal of Medicine* 383 (2020): 1328–1339, https://doi.org/10.1056/NEJMoa1917346.

26. S. Novello, D. M. Kowalski, A. Luft, et al., "Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study," *Journal of Clinical Oncology* 41, no. 11 (2023): 1999–2006, https://doi.org/10.1200/jco.22.01990.

27. M. C. Garassino, S. Gadgeel, G. Speranza, et al., "Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study," *Journal of Clinical Oncology* 41, no. 11 (2023): 1992–1998, https://doi.org/10.1200/jco.22.01989.

28. Z. Xu, H. Zhang, G. Ma, et al., "Real-World Evidence of Advanced Non-Small Cell Lung Carcinoma Treated With an Immune Checkpoint Inhibitor Plus Chemotherapy," *Oncology Letters* 28, no. 3 (2024): 405, https://doi.org/10.3892/ol.2024.14538.

29. C. Zhang, J. Shao, X. Tang, et al., "The Real-World Treatment Characteristic and Efficacy of Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Data From a Retrospective Cohort Study," *International Immunopharmacology* 134 (2024): 112152, https://doi.org/10.1016/j.intimp.2024.112152.

30. H. Kim, S. Kim, S. Choi, et al., "Clinical Validation of Artificial Intelligence-Powered PD-L1 Tumor Proportion Score Interpretation for Immune Checkpoint Inhibitor Response Prediction in Non-Small Cell Lung Cancer," *JCO Precision Oncology* 8 (2024): e2300556, https://doi.org/10.1200/po.23.00556.

31. M. Akhtar, S. Rashid, and I. A. Al-Bozom, "PD-L1 Immunostaining: What Pathologists Need to Know," *Diagnostic Pathology* 16 (2021): 94, https://doi.org/10.1186/s13000-021-01151-x.

32. H. Kim and J. H. Chung, "PD-L1 Testing in Non-Small Cell Lung Cancer: Past, Present, and Future," *Journal of Pathology and Translational Medicine* 53 (2019): 199–206, https://doi.org/10.4132/jptm.2019.04.24.

33. K. Ancevski Hunter, M. A. Socinski, and L. C. Villaruz, "PD-L1 Testing in Guiding Patient Selection for PD-1/PD-L1 Inhibitor Therapy in Lung Cancer," *Molecular Diagnosis & Therapy* 22 (2018): 1–10, https://doi.org/10.1007/s40291-017-0308-6.

34. M. Hersom and J. T. Jorgensen, "Companion and Complementary Diagnostics-Focus on PD-L1 Expression Assays for PD-1/PD-L1 Checkpoint Inhibitors in Non-Small Cell Lung Cancer," *Therapeutic Drug Monitoring* 40 (2018): 9–16, https://doi.org/10.1097/FTD.0000000000000460.

35. R. Buttner, J. R. Gosney, B. G. Skov, et al., "Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer," *Journal of Clinical Oncology* 35 (2017): 3867–3876, https://doi.org/10.1200/JCO.2017.74.7642.

36. China NMPA Approves VENTANA PD-L1 (SP263) Assay, https://www.nmpa.gov.cn/datasearch/search-info.html?nmpa=aWQ9OGE4ODdiZjQ2MGUzZmQyOTAxNjBlNDA1ODU4MzAwMjAmaXRlbUlkPWZmODA4MDgxODMwYjEwMzUwMTgzOGQ0ODcxYjUzNTQz.

37. "Chinese Expert Consensus on Standards of PD-L1 Immunohistochemistry Testing for Non-Small Cell Lung Cancer," *Zhongguo Fei Ai Za Zhi* 23 (2020): 733–740, https://doi.org/10.3779/j.issn.1009-3419.2020.101.43.

38. L. Y. Xue, Y. Li, J. Huang, et al., "Expert Consensus on PD-L1 Expression Testing in Esophageal Carcinoma in China," *Zhonghua Zhong Liu Za Zhi* 45 (2023): 291–297, https://doi.org/10.3760/cma.j.cn112152-20221129-00792.

39. M. Mino-Kenudson, N. Le Stang, J. B. Daigneault, et al., "The International Association for the Study of Lung Cancer Global Survey on Programmed Death-Ligand 1 Testing for NSCLC," *Journal of Thoracic Oncology* 16 (2021): 686–696, https://doi.org/10.1016/j.jtho.2020.12.026.

40. Y. Wu, L. Tao, L. Chang, F. Wang, S. Sun, and H. Sam, "EE303 Cost-Effectiveness Analysis of Pd-L1 Testing Associated With Pembrolizumab for First-Line Treatment of Advanced NSCLC in China," *Value in Health* 26, no. 6 (2023): S114, https://doi.org/10.1016/j.jval.2023.03.604.

41. Q. Liu, X. Luo, Z. Zhou, et al., "PD-L1 Test-Based Strategy With Nivolumab as the Second-Line Treatment in Advanced NSCLC: A Cost-Effectiveness Analysis in China," *Frontiers in Oncology* 11 (2021): 745493, https://doi.org/10.3389/fonc.2021.745493.

42. J. R. Gosney, A. M. Boothman, M. Ratcliffe, and K. M. Kerr, "Cytology for PD-L1 Testing: A Systematic Review," *Lung Cancer* 141 (2020): 101–106, https://doi.org/10.1016/j.lungcan.2020.01.010.

43. J. He, X. Wang, L. Cai, et al., "Effect of Storage Time of Paraffin Sections on the Expression of PD-L1 (SP142) in Invasive Breast Cancer," *Diagnostic Pathology* 18, no. 1 (2023): 131, https://doi.org/10.1186/s13000-023-01423-8.

44. S. Wen, L. Dai, L. Wang, et al., "Genomic Signature of Driver Genes Identified by Target Next-Generation Sequencing in Chinese Non-Small Cell Lung Cancer," *Oncologist* 24, no. 11 (2019): e1070–e1081, https://doi.org/10.1634/theoncologist.2018-0572.

45. J. T. Jørgensen and M. Hersom, "Clinical and Regulatory Aspects of Companion Diagnostic Development in Oncology," *Clinical Pharmacology and Therapeutics* 103 (2018): 999–1008, https://doi.org/10.1002/cpt.955.

46. K. Johrens and J. Ruschoff, "The Challenge to the Pathologist of PD-L1 Expression in Tumor Cells of Non-Small-Cell Lung Cancer—An Overview," *Current Oncology* 28 (2021): 5227–5239, https://doi.org/10.3390/curroncol28060437.

47. Y. Jin, Q. Xue, X. Shen, et al., "PD-L1 Expression and Comprehensive Molecular Profiling Predict Survival in Non-Small Cell Lung Cancer: A Real-World Study of a Large Chinese Cohort," *Clinical Lung Cancer* 23, no. 1 (2022): 43–51, https://doi.org/10.1016/j.cllc.2021.08.009.

48. Q. Zheng, Y. Huang, X. Zeng, et al., "Clinicopathological and Molecular Characteristics Associated With PD-L1 Expression in Non-Small Cell Lung Cancer: A Large-Scale, Multi-Center, Real-World Study in China," *Journal of Cancer Research and Clinical Oncology* 147, no. 5 (2021): 1547–1556, https://doi.org/10.1007/s00432-020-03444-y.

49. G. Troncone and C. Gridelli, "The Reproducibility of PD-L1 Scoring in Lung Cancer: Can the Pathologists Do Better?," *Translational Lung Cancer Research* 6 (2017): S74–s77, https://doi.org/10.21037/tlcr.2017.10.05.

50. E. S. Reisenbichler, G. Han, A. Bellizzi, et al., "Prospective Multi-Institutional Evaluation of Pathologist Assessment of PD-L1 Assays for Patient Selection in Triple Negative Breast Cancer," *Modern Pathology* 33, no. 9 (2020): 1746–1752, https://doi.org/10.1038/s41379-020-0544-x.

51. S. Chang, H. K. Park, Y. L. Choi, and S. J. Jang, "Interobserver Reproducibility of PD-L1 Biomarker in Non-Small Cell Lung Cancer: A Multi-Institutional Study by 27 Pathologists," *Journal of Pathology and Translational Medicine* 53, no. 6 (2019): 347–353, https://doi.org/10.4132/jptm.2019.09.29.

52. W. A. Cooper, P. A. Russell, M. Cherian, et al., "Intra- and Interobserver Reproducibility Assessment of PD-L1 Biomarker in Non-Small Cell Lung Cancer," *Clinical Cancer Research* 23, no. 16 (2017): 4569–4577, https://doi.org/10.1158/1078-0432.Ccr-17-0151.

53. B. Jasani, G. Banfer, R. Fish, et al., "Evaluation of an Online Training Tool for Scoring Programmed Cell Death Ligand-1 (PD-L1) Diagnostic Tests for Lung Cancer," *Diagnostic Pathology* 15, no. 37 (2020): 20200417, https://doi.org/10.1186/s13000-020-00953-9.

54. Y. Wang, A. Castelli, Q. Cao, and D. Liu, "Assessing the Design of China's Complex Health System - Concerns on Equity and Efficiency," *Health Policy Open* 1 (2020): 100021, https://doi.org/10.1016/j.hpopen.2020.100021.

55. H. Yan, Z. Han, H. Nie, et al., "Continuing Medical Education in China: Evidence From Primary Health Workers' Preferences for Continuing Traditional Chinese Medicine Education," *BMC Health Services Research* 23, no. 1 (2023): 1200, https://doi.org/10.1186/s12913-023-10153-y.

56. Z. H. Lu and J. Chen, "National Pathology Quality Report in 2019," *Zhonghua Bing Li Xue Za Zhi* 49 (2020): 667–669, https://doi.org/10.3760/cma.j.cn112151-20200331-00273.

57. K. S. Wang, G. Yu, C. Xu, et al., "Accurate Diagnosis of Colorectal Cancer Based on Histopathology Images Using Artificial Intelligence," *BMC Medicine* 19, no. 1 (2021): 76, https://doi.org/10.1186/s12916-021-01942-5.

58. D. L. Rimm, G. Han, J. M. Taube, et al., "A Prospective, Multi-Institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non-Small Cell Lung Cancer," *JAMA Oncology* 3 (2017): 1051–1058, https://doi.org/10.1001/jamaoncol.2017.0013.

59. J. Yeong, H. Y. J. Lum, C. B. Teo, et al., "Choice of PD-L1 Immunohistochemistry Assay Influences Clinical Eligibility for Gastric Cancer Immunotherapy," *Gastric Cancer* 25, no. 4 (2022): 741–750, https://doi.org/10.1007/s10120-022-01301-0.

60. M. Udall, M. Rizzo, J. Kenny, et al., "PD-L1 Diagnostic Tests: A Systematic Literature Review of Scoring Algorithms and Test-Validation Metrics," *Diagnostic Pathology* 13, no. 1 (2018): 12, https://doi.org/10.1186/s13000-018-0689-9.

61. L. M. Sholl, M. Awad, U. Basu Roy, et al., "Programmed Death Ligand-1 and Tumor Mutation Burden Testing of Patients With Lung Cancer for Selection of Immune Checkpoint Inhibitor Therapies: Guideline From the College of American Pathologists, Association for Molecular Pathology, International Association for the Study of Lung Cancer, Pulmonary Pathology Society, and LUNGevity Foundation," *Archives of Pathology & Laboratory Medicine* 148 (2024): 757–774, https://doi.org/10.5858/arpa.2023-0536-CP.

62. M. D. Keller, C. Neppl, Y. Irmak, et al., "Adverse Prognostic Value of PD-L1 Expression in Primary Resected Pulmonary Squamous Cell Carcinomas and Paired Mediastinal Lymph Node Metastases," *Modern Pathology* 31, no. 1 (2018): 101–110, https://doi.org/10.1038/modpathol.2017.111.

63. S. Kim, J. Koh, D. Kwon, et al., "Comparative Analysis of PD-L1 Expression Between Primary and Metastatic Pulmonary Adenocarcinomas," *European Journal of Cancer* 75 (2017): 141–149, https://doi.org/10.1016/j.ejca.2017.01.004.

64. E. Munari, G. Zamboni, G. Lunardi, et al., "PD-L1 Expression Comparison Between Primary and Relapsed Non-Small Cell Lung Carcinoma Using Whole Sections and Clone SP263," *Oncotarget* 9, no. 54 (2018): 30465–30471, https://doi.org/10.18632/oncotarget.25770.

65. H. Uruga, E. Bozkurtlar, T. G. Huynh, et al., "Programmed Cell Death Ligand (PD-L1) Expression in Stage II and III Lung Adenocarcinomas and Nodal Metastases," *Journal of Thoracic Oncology* 12, no. 3 (2017): 458–466, https://doi.org/10.1016/j.jtho.2016.10.015.

66. D. Casadevall, S. Clavé, Á. Taus, et al., "Heterogeneity of Tumor and Immune Cell PD-L1 Expression and Lymphocyte Counts in Surgical NSCLC Samples," *Clinical Lung Cancer* 18, no. 6 (2017): 682–691, https://doi.org/10.1016/j.cllc.2017.04.014.

67. Z. Y. Dong, C. Zhang, Y. F. Li, et al., "Genetic and Immune Profiles of Solid Predominant Lung Adenocarcinoma Reveal Potential Immunotherapeutic Strategies," *Journal of Thoracic Oncology* 13, no. 1 (2018): 85–96, https://doi.org/10.1016/j.jtho.2017.10.020.

68. J. Liu, Q. Zheng, X. Mu, et al., "Automated Tumor Proportion Score Analysis for PD-L1 (22C3) Expression in Lung Squamous Cell Carcinoma," *Scientific Reports* 11, no. 1 (2021): 15907, https://doi.org/10.1038/s41598-021-95372-1.

69. A. H. Scheel, M. Dietel, L. C. Heukamp, et al., "Harmonized PD-L1 Immunohistochemistry for Pulmonary Squamous-Cell and Adenocarcinomas," *Modern Pathology* 29, no. 10 (2016): 1165–1172, https://doi.org/10.1038/modpathol.2016.117.

70. J. Adam, N. Le Stang, I. Rouquette, et al., "Multicenter Harmonization Study for PD-L1 IHC Testing in Non-Small-Cell Lung Cancer," *Annals of Oncology* 29 (2018): 953–958, https://doi.org/10.1093/annonc/mdy014.

71. Tumor Pathology Committee of Chinese Anti-Cancer A, Expert Committee on Pathology of Chinese Society of Clinical O, and Expert Committee on Non-Small Cell Lung Cancer of Chinese Society of Clinical O, "Expert Consensus on PD-L1 Expression Testing in Non-Small-Cell Lung Cancer in China," *Zhonghua Zhong Liu Za Zhi* 42 (2020): 513–521, https://doi.org/10.3760/cma.j.cn112152-20200313-00202.

72. J. Wang, B. Zhang, L. Peng, et al., "Chinese Expert Consensus Recommendations for the Administration of Immune Checkpoint Inhibitors to Special Cancer Patient Populations," *Therapeutic Advances in Medical Oncology* 15 (2023): 1–22, https://doi.org/10.1177/17588359231187205.

73. F. R. Hirsch, A. McElhinny, D. Stanforth, et al., "PD-L1 Immunohistochemistry Assays for Lung Cancer: Results From Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project," *Journal of Thoracic Oncology* 12, no. 2 (2017): 208–222, https://doi.org/10.1016/j.jtho.2016.11.2228.

74. M. S. Tsao, K. M. Kerr, M. Kockx, et al., "PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project," *Journal of Thoracic Oncology* 13, no. 9 (2018): 1302–1311, https://doi.org/10.1016/j.jtho.2018.05.013.

75. Q. Yang, M. Chen, J. Gu, et al., "Novel Biomarkers of Dynamic Blood PD-L1 Expression for Immune Checkpoint Inhibitors in Advanced

Non-Small-Cell Lung Cancer Patients," *Frontiers in Immunology* 12 (2021): 665133, https://doi.org/10.3389/fimmu.2021.665133.

76. M. P. Humphries, V. Bingham, F. Abdullahi Sidi, et al., "Improving the Diagnostic Accuracy of the PD-L1 Test With Image Analysis and Multiplex Hybridization," *Cancers (Basel)* 12 (2020): 20200429, https://doi.org/10.3390/cancers12051114.

77. J. Adam, V. Hofman, A. Mansuet-Lupo, et al., "P2.09-17 Real-World Concordance Across Pathologists for PD-L1 Scoring in Non-Small Cell Lung Cancer: Results From a Large Nationwide Initiative," *Journal of Thoracic Oncology* 14 (2019): S775, https://doi.org/10.1016/j.jtho.2019.08.1666.

78. S. Althammer, T. H. Tan, A. Spitzmuller, et al., "Automated Image Analysis of NSCLC Biopsies to Predict Response to Anti-PD-L1 Therapy," *Journal for Immunotherapy of Cancer* 7, no. 121 (2019): 20190506, https://doi.org/10.1186/s40425-019-0589-x.

79. V. Baxi, G. Lee, C. Duan, et al., "Association of Artificial Intelligence-Powered and Manual Quantification of Programmed Death-Ligand 1 (PD-L1) Expression With Outcomes in Patients Treated With Nivolumab ± Ipilimumab," *Modern Pathology* 35, no. 11 (2022): 1529–1539, https://doi.org/10.1038/s41379-022-01119-2.

80. J. R. Naso, T. Povshedna, G. Wang, et al., "Automated PD-L1 Scoring for Non-Small Cell Lung Carcinoma Using Open-Source Software," *Pathology Oncology Research* 27 (2021): 609717, https://doi.org/10.3389/pore.2021.609717.

81. B. Pan, Y. Kang, Y. Jin, et al., "Automated Tumor Proportion Scoring for PD-L1 Expression Based on Multistage Ensemble Strategy in Non-Small Cell Lung Cancer," *Journal of Translational Medicine* 19, no. 1 (2021): 249, https://doi.org/10.1186/s12967-021-02898-z.

82. G. Cheng, F. Zhang, Y. Xing, et al., "Artificial Intelligence-Assisted Score Analysis for Predicting the Expression of the Immunotherapy Biomarker PD-L1 in Lung Cancer," *Frontiers in Immunology* 13 (2022): 893198, https://doi.org/10.3389/fimmu.2022.893198.

83. Z. Huang, L. Chen, L. Lv, et al., "A New AI-Assisted Scoring System for PD-L1 Expression in NSCLC," *Computer Methods and Programs in Biomedicine* 221 (2022): 106829, https://doi.org/10.1016/j.cmpb.2022.106829.

84. M. Griffin, M. Gemici, A. Javed, et al., "Abstract 471: AIM PD-L1-NSCLC: Artificial Intelligence-Powered PD-L1 Quantification for Accurate Prediction of Tumor Proportion Score in Diverse, Multi-Stain Clinical Tissue Samples," *Cancer Research* 82 (2022): 471, https://doi.org/10.1158/1538-7445.AM2022-471.

85. J. Wu, C. Liu, X. Liu, et al., "Artificial Intelligence-Assisted System for Precision Diagnosis of PD-L1 Expression in Non-Small Cell Lung Cancer," *Modern Pathology* 35, no. 3 (2022): 403–411, https://doi.org/10.1038/s41379-021-00904-9.

86. C. H. Lim, Y. W. Koh, S. H. Hyun, et al., "A Machine Learning Approach Using PET/CT-Based Radiomics for Prediction of PD-L1 Expression in Non-Small Cell Lung Cancer," *Anticancer Research* 42 (2022): 5875–5884, https://doi.org/10.21873/anticanres.16096.

87. X. Zhao, Y. Zhao, J. Zhang, Z. Zhang, and L. Liu, "Predicting PD-L1 Expression Status in Patients With Non-Small Cell Lung Cancer Using [18F]FDG PET/CT Radiomics," *EJNMMI Research* 13, no. 1 (2023): 4, https://doi.org/10.1186/s13550-023-00956-9.

88. H. Kim, S. Choi, S. Kim, et al., "Clinical Performance of Artificial Intelligence-Powered Annotation of Tumor Cell PD-L1 Expression for Treatment of Immune-Checkpoint Inhibitor (ICI) in Advanced Non-Small Cell Lung Cancer (NSCLC)," *Journal of Clinical Oncology* 39 (2021): 9026, https://doi.org/10.1200/JCO.2021.39.15_suppl.9026.

89. P. Vaidya, K. Bera, P. D. Patil, et al., "Novel, Non-Invasive Imaging Approach to Identify Patients With Advanced Non-Small Cell Lung Cancer at Risk of Hyperprogressive Disease With Immune Checkpoint Blockade," *Journal for Immunotherapy of Cancer* 8, no. 2 (2020): e001343, https://doi.org/10.1136/jitc-2020-001343.

90. W. Mu, L. Jiang, Y. Shi, et al., "Non-Invasive Measurement of PD-L1 Status and Prediction of Immunotherapy Response Using Deep Learning of PET/CT Images," *Journal for Immunotherapy of Cancer* 9, no. 6 (2021): e002118, https://doi.org/10.1136/jitc-2020-002118.

91. S. M. Shavarani, M. López-Ibáñez, R. Allmendinger, and J. Knowles, "An Interactive Decision Tree-Based Evolutionary Multi-Objective Algorithm," in *Evolutionary Multi-Criterion Optimization*, ed. M. Emmerich, A. Deutz, H. Wang, et al. (Springer Nature Switzerland, 2023), 620–634.

92. A. J. Larrazabal, N. Nieto, V. Peterson, D. H. Milone, and E. Ferrante, "Gender Imbalance in Medical Imaging Datasets Produces Biased Classifiers for Computer-Aided Diagnosis," *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 23 (2020): 12592–12594, https://doi.org/10.1073/pnas.1919012117.

93. M. Belkin, D. Hsu, S. Ma, and S. Mandal, "Reconciling Modern Machine-Learning Practice and the Classical Bias-Variance Trade-Off," *Proceedings of the National Academy of Sciences of the United States of America* 116, no. 32 (2019): 15849–15854, https://doi.org/10.1073/pnas.1903070116.

94. J. T. Shreve, S. A. Khanani, and T. C. Haddad, "Artificial Intelligence in Oncology: Current Capabilities, Future Opportunities, and Ethical Considerations," *American Society of Clinical Oncology Educational Book* 42 (2022): 1–10, https://doi.org/10.1200/EDBK_350652.

95. F. McKay, B. J. Williams, G. Prestwich, D. Bansal, N. Hallowell, and D. Treanor, "The Ethical Challenges of Artificial Intelligence-Driven Digital Pathology," *Journal of Pathology. Clinical Research* 8, no. 3 (2022): 209–216, https://doi.org/10.1002/cjp2.263.

96. P. Hacker, "The European AI Liability Directives – Critique of a Half-Hearted Approach and Lessons for the Future," *Computer Law and Security Review* 51 (2023): 105871, https://doi.org/10.1016/j.clsr.2023.105871.

97. B. Solaiman and A. Malik, "Regulating Algorithmic Care in the European Union: Evolving Doctor-Patient Models Through the Artificial Intelligence Act (AI-Act) and the Liability Directives," *Medical Law Review* 33 (2025): 33, https://doi.org/10.1093/medlaw/fwae033.

98. J. G. Yao and H. Bu, "Call Attention to the Overall Benefit of Digital Pathology and Promote Its Development," *Zhonghua Bing Li Xue Za Zhi* 53 (2024): 116–120, https://doi.org/10.3760/cma.j.cn112151-20230831-00112.

99. D. D. Xiong, R. Q. He, Z. G. Huang, et al., "Global Bibliometric Mapping of the Research Trends in Artificial Intelligence-Based Digital Pathology for Lung Cancer Over the Past Two Decades," *Digital Health* 10 (2024): 1–13, https://doi.org/10.1177/20552076241277735.

100. J. He, S. L. Baxter, J. Xu, X. Zhou, and K. Zhang, "The Practical Implementation of Artificial Intelligence Technologies in Medicine," *Nature Medicine* 25, no. 1 (2019): 30–36, https://doi.org/10.1038/s41591-018-0307-0.

101. F. Wu, C. Lu, M. Zhu, et al., "Towards a New Generation of Artificial Intelligence in China," *Nature Machine Intelligence* 2 (2020): 312–316, https://doi.org/10.1038/s42256-020-0183-4.

102. M. Cui and D. Y. Zhang, "Artificial Intelligence and Computational Pathology," *Laboratory Investigation* 101 (2021): 412–422, https://doi.org/10.1038/s41374-020-00514-0.

103. D. A. Hashimoto, G. Rosman, D. Rus, and O. R. Meireles, "Artificial Intelligence in Surgery: Promises and Perils," *Annals of Surgery* 268 (2018): 70–76, https://doi.org/10.1097/SLA.0000000000002693.

104. J. Ruan, Z. Zhu, C. Wu, G. Ye, J. Zhou, and J. Yue, "A Fast and Effective Detection Framework for Whole-Slide Histopathology Image Analysis," *PLoS One* 16, no. 5 (2021): e0251521, https://doi.org/10.1371/journal.pone.0251521.

105. L. Pantanowitz, J. H. Sinard, W. H. Henricks, et al., "Validating Whole Slide Imaging for Diagnostic Purposes in Pathology: Guideline

From the College of American Pathologists Pathology and Laboratory Quality Center," *Archives of Pathology & Laboratory Medicine* 137, no. 12 (2013): 1710–1722, https://doi.org/10.5858/arpa.2013-0093-CP.

106. B. J. Williams and D. Treanor, "Practical Guide to Training and Validation for Primary Diagnosis With Digital Pathology," *Journal of Clinical Pathology* 73 (2020): 418–422, https://doi.org/10.1136/jclinpath-2019-206319.

107. J. Chen, Y. Jiao, C. Lu, J. Zhou, Z. Zhang, and C. Zhou, "A Nationwide Telepathology Consultation and Quality Control Program in China: Implementation and Result Analysis," *Diagnostic Pathology* 9 Suppl 1, no. Suppl 1 (2014): S2, https://doi.org/10.1186/1746-1596-9-S1-S2.

108. J. C. Hutchinson, J. Picarsic, C. McGenity, et al., "Whole Slide Imaging, Artificial Intelligence, and Machine Learning in Pediatric and Perinatal Pathology: Current Status and Future Directions," *Pediatric and Developmental Pathology* 28, no. 2 (2024): 20241118, https://doi.org/10.1177/10935266241299073.

109. C. Silcox, E. Zimlichmann, K. Huber, et al., "The Potential for Artificial Intelligence to Transform Healthcare: Perspectives From International Health Leaders," *NPJ Digital Medicine* 7, no. 1 (2024): 88, https://doi.org/10.1038/s41746-024-01097-6.

110. S. Vos, K. Hebeda, M. Milota, et al., "Making Pathologists Ready for the New Artificial Intelligence Era: Changes in Required Competencies," *Modern Pathology* 38, no. 2 (2025): 100657, https://doi.org/10.1016/j.modpat.2024.100657.

111. B. Ricciuti, X. Wang, J. V. Alessi, et al., "Association of High Tumor Mutation Burden in Non-Small Cell Lung Cancers With Increased Immune Infiltration and Improved Clinical Outcomes of PD-L1 Blockade Across PD-L1 Expression Levels," *JAMA Oncology* 8 (2022): 1160–1168, https://doi.org/10.1001/jamaoncol.2022.1981.

112. N. Li, Z. Wan, D. Lu, R. Chen, and X. Ye, "Long-Term Benefit of Immunotherapy in a Patient With Squamous Lung Cancer Exhibiting Mismatch Repair Deficient/High Microsatellite Instability/High Tumor Mutational Burden: A Case Report and Literature Review," *Frontiers in Immunology* 13 (2022): 1088683, https://doi.org/10.3389/fimmu.2022.1088683.

113. T. Kanai, H. Suzuki, H. Yoshida, et al., "Significance of Quantitative Interferon-Gamma Levels in Non-Small-Cell Lung Cancer Patients' Response to Immune Checkpoint Inhibitors," *Anticancer Research* 40 (2020): 2787–2793, https://doi.org/10.21873/anticanres.14251.

114. J. Mei, G. Jiang, Y. Chen, et al., "HLA Class II Molecule HLA-DRA Identifies Immuno-Hot Tumors and Predicts the Therapeutic Response to Anti-PD-1 Immunotherapy in NSCLC," *BMC Cancer* 22, no. 1 (2022): 738, https://doi.org/10.1186/s12885-022-09840-6.