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Review Article

Transbronchial Cryobiopsy in the Era of Precision Thoracic Diagnostics: Histopathology, Omics, Radiomics, and AI Converge", Narrative Review

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Abstract:

Transbronchial cryobiopsy (TBCB) represents one of the most significant innovations in recent years in the diagnosis of diffuse lung diseases and thoracic malignancies. This technique, which involves the use of a cryoprobe introduced endoscopically, enables the collection of large, well-preserved tissue samples free from compression artifacts, thus overcoming the limitations of traditional forceps biopsies and providing a less invasive alternative to surgical lung biopsy. The retrieved tissues are ideal not only for histopathological evaluation but also for advanced molecular analyses, including next-generation sequencing (NGS), transcriptomics (RNA-seq), epigenomics, and proteomic profiling, positioning TBCB as a key tool in thoracic precision medicine. In light of current evidence, TBCB emerges not only as a high-value biopsy technique but also as a strategic technological platform for integrated morphological and molecular diagnosis, paving the way for a more equitable, timely, and personalized approach to the management of complex pulmonary diseases. This paper provides a critical and multidimensional review of the emerging applications of TBCB, encompassing its role in the integrated diagnosis of interstitial lung diseases (ILDs), in the molecular characterization of non-small cell lung cancer (NSCLC), in the identification of emerging biomarkers, and in synergy with advanced technologies such as radiomics and artificial intelligence. Particular attention is given to the use of TBCB in clinically fragile populations, including children, the elderly, and patients with severe comorbidities, highlighting its favourable safety profile, risk mitigation strategies, and the high quality of tissue samples obtainable even in these delicate clinical settings.

Key words: transbronchial cryobiopsy (tbcb); interstitial lung diseases (ild); non-small cell lung cancer (nsclc); molecular profiling; artificial intelligence (ai); radiomics

Abbreviation:

PD-L1, Programmed Death Ligand-1; **TBCB,** Transbronchial CryoBiopsy; **ILD,** Interstitial Lung Diseases; **NSCLC,** Non-Small Cell Lung Cancer; **NGS,** Next-Generation Sequencing; **RNA**-seq, RNA Sequencing; **scRNA-seq,** Single-cell RNA Sequencing; **TMB,** Tumor

Mutational Burden; **UIP,** Usual Interstitial Pneumonia; **NSIP,** Nonspecific Interstitial Pneumonia; **OP,** Organizing Pneumonia; **HP,** Hypersensitivity Pneumonitis; **HRCT,** High-Resolution Computed Tomography; **AI** Artificial Intelligence, ; **CNN,** Convolutional Neural Network; **SLB,** Surgical Lung Biopsy; **TBB**, Transbronchial Biopsy; TBNA, Transbronchial Needle Aspiration; VATS, Video-Assisted Thoracoscopic Surgery; ATS, American Thoracic Society; **ERS,** European Respiratory Society; **CHEST,** American College of Chest Physicians; **ALAT,** Latin American Thoracic Society; **MDD,** Multidisciplinary Discussion; **MDT,** Multidisciplinary Team; **miRNA,** microRNA; **FISH,** Fluorescence In Situ Hybridization; **EBUS,** Endobronchial Ultrasound; **DLCO,** Diffusing Capacity of the Lung for Carbon Monoxide; **KL-6,** Krebs von den Lungen-6; **TILs,** Tumor-Infiltrating Lymphocytes; **AUC,** Area Under the Curve.

1. Introduction

Ice, in its various forms, plays a fundamental role in modern medicine, both as a tool for cryopreservation and as a therapeutic agent. In cryopreservation, ultra-low temperatures are used to preserve biological tissues, cells, and even organs, maintaining their structural and molecular integrity for future diagnostic or therapeutic use. This is essential in biobanking, fertility treatments, and transplant medicine. Clinically, cold is employed in techniques such as cryotherapy and cryoablation, where extreme cold is applied to destroy abnormal or pathological tissues, including tumors, with precision and minimal invasiveness. As Haruki Murakami reflects in his book *Blind Willow, Sleeping Woman*, "Ice can preserve everything… cleanly and clearly"; a poetic truth that highlights its unique and evolving role in healthcare and particularly in diagnostics, where Transbronchial Cryobiopsy (TBCB) has emerged in recent years as a key tool in the diagnosis of diffuse lung diseases and thoracic malignancies. Compared to conventional forceps biopsy, it provides significantly larger samples with preserved architecture and higher cellularity, improving both histopathological and molecular analysis, including its use in Next-Generation Sequencing techniques.

This work aims to provide an updated, in-depth, and multidisciplinary review of the use of this novel tool in diffuse lung diseases and thoracic tumors. Not only will the technical and safety aspects of the procedure be examined in detail, but also its applications in precision medicine, integration with omics sciences and radiomics, its potential role in the validation of emerging biomarkers, and the impact of digital pathology and artificial intelligence in the automated reading of histological slides.

In an era where pulmonology is increasingly moving toward a personalized, predictive, and integrated model, TBCB stands not only as a diagnostic tool but also as a technological and conceptual pillar of the new era of precision pulmonology [1].

The methodological approach involved an extensive electronic literature search through Medline, Embase, Cochrane, and PubMed databases, including publications up to January 1st, 2025. Keywords such as "lung cryobiopsy," "transbronchial biopsy," "interstitial lung diseases," "ILD," "histologic diagnosis," "bronchoscopy," "interventional pulmonology," "molecular analysis," and "transcriptomics" were used, combined with terms like "diagnostic accuracy" and "procedural safety" using Boolean operators, to ensure a broad and inclusive search strategy. This methodology enabled the identification of a wide range of relevant literature, from pioneering studies to the most recent contributions on the use of cryobiopsy in clinical practice and in the context of advanced molecular applications, including transcriptomic studies on tissue samples obtained using this technique.

2.Transbronchial Cryobiopsy: Mechanism, Procedure, and Complications

TBCB has become a standardized procedure in many clinical settings, offering a reliable and minimally invasive approach for obtaining high-quality samples. It enables the collection of **larger and well-preserved tissue specimens**, suitable for both histological evaluation and advanced molecular analyses. With its growing adoption in pulmonology, TBCB is now included in clinical guidelines and recommended for the diagnosis of various pulmonary diseases, including interstitial lung diseases (ILDs) and thoracic malignancies [2].

TBCB involves the use of a flexible cryoprobe, typically 1.9 mm or 2.4 mm in diameter, inserted through the working channel of a flexible bronchoscope. Both probes provide comparable diagnostic yield, but the 1.9 mm probe is associated with a lower rate of complications—particularly pneumothorax—and allows easier access to peripheral regions of the lung. In contrast, the 2.4 mm probe may increase the risk of adverse events without significantly improving diagnostic performance [3–4].

Under fluoroscopic guidance or, in some cases, with the assistance of endobronchial ultrasound (EBUS), the cryoprobe is advanced into the target area of the lung parenchyma. The tip of the probe reaches −89.5 °C, allowing for rapid freezing of the target tissue and secure adherence for extraction [3]. Once positioned, the probe is activated for a freezing time typically between 3 and 7 seconds, inducing rapid adhesion and freezing of the surrounding tissue. The bronchoscope and cryoprobe are then withdrawn together, extracting a large and well-preserved lung sample. The freezing process induces haemostasis in the small vessels of the deep lung, although it may still cause bleeding or pleural damage, potentially resulting in pneumothorax. To minimize the risk of bleeding, a bronchial blocker or Fogarty balloon is generally pre-positioned in the sampled bronchial segment and inflated immediately after the biopsy.

Fluoroscopy plays a key role in enhancing the safety and accuracy of TBCB. This real-time imaging technique allows visualization of the cryoprobe's position within the bronchial tree and guides it precisely to the desired segment. During the procedure, fluoroscopy is used to ensure that the probe tip is located at a safe distance from the pleura—typically 1–2 cm—to reduce the risk of pleural injury and pneumothorax. It also helps to avoid overly central sampling, which increases the risk of bleeding due to proximity to larger vessels. Once the probe is correctly positioned, activation proceeds.

TBCB can be performed via flexible bronchoscopy under moderate-to-deep sedation or in combination with rigid bronchoscopy under general anesthesia, depending on the patient's clinical condition and the team's experience or preference. Flexible bronchoscopy is generally used in stable patients and in centers with well-established expertise, offering a less invasive and well-tolerated option. However, in cases with a higher risk of complications—such as anticipated bleeding, airway management difficulties, or the need for multiple samples—rigid bronchoscopy is preferred, as it provides better airway control, larger channels, greater suction capacity, and the possibility to introduce flexible instruments and haemostatic devices.

During the procedure, the rigid bronchoscope is inserted under general anaesthesia to maintain airway patency. Through the rigid bronchoscope, the flexible cryoprobe is guided to the target segment under fluoroscopic guidance. The probe is activated (typically for 3–6 seconds), freezing the target tissue, and then withdrawn together with the flexible bronchoscope, while the rigid bronchoscope remains in place to maintain airway access. The pre-positioned bronchial balloon is inflated immediately afterward to control any bleeding.

Nevertheless, there are inherent risks. The most common complications are bleeding (ranging from mild to severe) and pneumothorax, with reported frequencies ranging from 0% to 30%, depending on the center's experience [4]. Therefore, TBCB should only be performed in centers with appropriate expertise, under close monitoring and with immediate availability for emergency intervention. Despite these risks, when properly performed, TBCB represents an excellent compromise between diagnostic yield and procedural safety.

3. High-Quality Tissue for Personalized Medicine: The Clinical Value of TBCB

TBCB is primarily indicated in the diagnostic workup of interstitial lung diseases (ILDs), especially when high-resolution computed tomography (HRCT) findings are inconclusive and multidisciplinary discussion suggests the need for histological confirmation. In recent years, the diagnosis of diffuse pulmonary diseases and intrathoracic malignancies has undergone a profound transformation, driven by the growing need to integrate classical morphological analysis with molecular and genomic tissue profiling, adopting a multidimensional, biomarker-guided approach [2,5]. This shift has highlighted the central role of biopsy techniques capable of providing high-quality tissue samples**,** a fundamental prerequisite for effective diagnosis and truly personalized therapeutic planning [4–6].

Compared to surgical lung biopsy (SLB)—considered the gold standard for ILD diagnosis but associated with high complication rates—TBCB demonstrated an 85% histopathological diagnostic yield in a retrospective study of 40 patients, with an average sample diameter of 5.7 ± 2 mm and a mean area of 40 ± 2 mm². These findings support its use as a less invasive alternative, although it remains associated with a non-negligible risk of bleeding, particularly in procedures performed via flexible endoscopy (60%) [7].

When combined with transbronchial lung biopsy (TBLB), TBCB significantly increases the diagnostic yield of flexible bronchoscopy in patients with diffuse parenchymal lung disease (DPLD), especially in ILD and hypersensitivity pneumonitis, potentially reducing the need for surgical biopsy while maintaining a notable risk of complications.

In a retrospective study of 56 patients with DPLD undergoing TBLB followed by TBCB in the same session, cryobiopsy yielded larger tissue samples (0.4–2.6 cm, average 2 samples per patient) compared to TBLB (0.1–0.8 cm, average 4 samples per patient), improving overall diagnostic yield: in 11 patients (20%), a diagnosis unattainable by TBLB alone was achieved, raising the total rate of definitive diagnosis to 46%. Reported complications included pneumothorax (20%) and massive hemoptysis (2%) [8].

Compared to forceps transbronchial lung biopsy (TBLB), which is limited by small sample size and frequent crush artifacts, cryoprobe-assisted TBLB has shown significantly better performance. In a randomized clinical trial involving 77 ILD patients, diagnostic yield was 51.3% in the cryoprobe group versus 29.1% in the forceps group ($P = 0.038$), with significantly larger sample areas (14.7 ± 11 mm² vs. 3.3 ± 4.1 mm²; $P < 0.001$) and no significant increase in haemorrhagic complications [9].

In this context, TBCB has emerged as an innovative and strategic solution, capable of combining high-quality histologic samples with a minimally invasive, well-tolerated, and repeatable approach, increasingly validated as an alternative to surgical biopsy in the management of diffuse parenchymal lung diseases—particularly when performed in expert centers using a multidisciplinary approach [10].

In efforts to optimize biopsy techniques and enhance diagnostic yield, a prospective study involving 46 DPLD patients showed that performing two biopsies from different segments within the same lobe significantly improved diagnostic yield up to 96%, compared to multiple biopsies from a single segment. This underscores the value of a targeted segmental sampling strategy [11].

These features have encouraged the expanding use of TBCB across various interventional pulmonology domains—from the differential diagnosis of ILDs to molecular profiling of lung cancers—enabling complex analyses such as NGS, RNA-seq, PD-L1 expression, and tumor mutational burden (TMB) assessment [14–15]. Cryobiopsy has provided tissue suitable for single-cell RNA sequencing, a powerful technology for identifying new cell populations and molecular pathways involved in pulmonary fibrosis, paving the way for personalized targeted therapies [12].

Moreover, the integration of cryobiopsy with genomic classifiers—assessing the expression of fibrosis-associated genes—allows the combination of morphological and gene expression analyses, significantly increasing diagnostic confidence in ILD cases with indeterminate patterns and reducing the need for surgical biopsy in appropriate clinical and radiological contexts [13].

In oncology, the combination of transbronchial cryobiopsy with EBUS-TBNA enabled effective mediastinal lymph node sampling in 29 of 32 cases (90.6%), with tumor content exceeding 30% in all malignant samples, and significantly greater DNA and RNA yields compared to cell blocks. A 100% success rate in molecular testing (RT-PCR or NGS) was achieved in 13 patients with NSCLC, melanoma, or sarcoma, with no clinically relevant complications [16]. Similarly, in peripheral lung lesions, cryobiopsy combined with Endobronchial Ultrasonography using a guide sheath (EBUS-GS) achieved an 87% diagnostic yield, with tissue volumes over 20 times larger than conventional biopsy (0.078 cm³ vs. 0.003 cm³; $p < 0.0001$), and successful DNA extraction for NGS in all cancer cases, with a mean DNA yield of 5.72 µg [17].

In a single-center retrospective study of 41 patients, transbronchial mediastinal cryobiopsy demonstrated an overall diagnostic yield of 95.1%, significantly higher than EBUS-TBNA (41.5%; $p < 0.001$), particularly for hematological disorders (100% vs. 28.6%), benign diseases (100% vs. 37.5%), and rare tumors (100% vs. 25%). The procedure was safe and well-tolerated, with only mild adverse events in 9.7% of cases and no need for escalation of care, even among patients with a Charlson Comorbidity Index ≥5 [70].

In oncology, a study showed that TBCB, when combined with forceps biopsy and cytological brushing, can achieve a total diagnostic yield of 94% in peripheral lung lesions suspected of malignancy, proving

particularly effective in the lower lobes (94.5%) and providing samples suitable for NGS analysis, with a 100% success rate [20].

Interest in transbronchial cryobiopsy is rapidly growing, driven by the emergence of advanced diagnostic approaches based on multi-omics technologies, artificial intelligence, and radiomics, all requiring high-quality tissue samples suitable for integrative analyses. This new biopsy technique has proven capable of meeting these demands, offering specimens suitable for morphological, transcriptomic, epigenetic, and microenvironmental studies within a single procedure, making it a central tool in the diagnosis of complex thoracic diseases.

Meanwhile, major international scientific societies (ATS, ERS, CHEST, ALAT) have recognized its clinical value in their guidelines [18], while recommending its use in experienced centers. Furthermore, its application is expanding to previously excluded populations, such as the elderly, pediatric patients, and individuals with significant comorbidities.

4. Transbronchial Cryobiopsy: diagnostic yield, safety, standardization, clinical evidence, and international recommendations

Multiple studies have confirmed that TBCB offers superior diagnostic yield compared to conventional transbronchial biopsy, even from a clinical perspective. In a randomized study involving 77 ILD patients, TBCB achieved a significantly higher histopathological diagnostic yield (74.4% vs. 34.1%, $P < 0.001$) and clinical yield (51.3% vs. 29.1%, $P = 0.038$), along with significantly larger tissue samples (14.7 ± 11 mm² vs. 3.3 ± 4.1 mm²; $P < 0.001$) [22]. These findings were confirmed by a meta-analysis of 916 patients, which demonstrated a significantly higher diagnostic yield for TBCB compared to transbronchial biopsy in both ILD and lung cancer, with a 36% relative improvement (RR = 1.36; $P = 0.0002$) [23–24].

In oncology, the application of TBCB for mediastinal lesions is still under investigation. A large randomized study of 197 patients with mediastinal lesions ≥1 cm showed that EBUS-guided TBCB achieved a significantly higher overall diagnostic yield than EBUS-TBNA (91.8% vs. 79.9%; $p = 0.001$), with clear advantages in rare tumors (91.7% vs. 25.0%; $p = 0.001$) and benign diseases (80.9% vs. 53.2%; $p = 0.004$), without a significant increase in complication rates [25]. However, in common lung cancers and metastatic lymphadenopathy, current data suggest similar diagnostic performance between TBCB, EBUS-TBNA, and forceps biopsy [26–27].

While TBCB shows a clear diagnostic advantage over conventional transbronchial biopsy, its potential superiority over video-assisted thoracoscopic surgery (VATS) remains debated. VATS continues to be regarded as the standard for histological evaluation of ILD, as demonstrated in a large retrospective study reporting a diagnostic yield of 98.7% for VATS compared to 82.8% for TBCB [29]. Consistently, a meta-analysis by Iftikhar et al. estimated average diagnostic yields of 83.7% for TBCB and 92.7% for VATS [30]. However, while the yield of TBCB is well-documented, its diagnostic accuracy remains less defined: several studies have shown low concordance between TBCB and VATS samples taken from the same anatomical site, raising concerns about the reliability of cryobiopsy as a standalone diagnostic tool [28, 31].

In this context, the COLDICE study [6] represents a methodological landmark. This prospective multicenter Australian study, published in 2019, was the first to directly compare the diagnostic accuracy of TBCB and VATS within the same patient. Sixty-five patients with suspected ILD underwent both biopsy techniques during the same anesthesia session. Samples were blindly reviewed by expert pathologists and subsequently discussed in a multidisciplinary team (MDT) to establish a final diagnosis. The study reported a diagnostic concordance of 70.8%, with a kappa coefficient of 0.70, indicating good agreement between the two techniques. Furthermore, TBCB demonstrated a significantly better safety profile than VATS, with fewer severe complications. These findings support its use as a valid, less invasive alternative to surgery—particularly in frail patients or when a conservative approach is preferred. The study also reinforced the central role of multidisciplinary evaluation and demonstrated that high-quality samples can be obtained through advanced endoscopic techniques when performed in experienced centers.

Although TBCB offers significant advantages in diagnostic yield and tissue quality, it is not without risks, particularly bleeding and pneumothorax. Comparative studies between cryoprobe-assisted TBLB and conventional forceps biopsy reported a higher incidence of grade 2 bleeding in the cryoprobe group (56.4% vs. 34.2%), although no significant differences in other complications were observed [9]. In general, the most common adverse events—bleeding and pneumothorax—are manageable via endoscopy or chest drainage and rarely require invasive interventions or prolonged hospital stays.

In a multicenter retrospective study of 276 ILD patients, TBCB demonstrated a significantly higher diagnostic yield compared to forceps biopsy (TBFB), both in fibrotic (74% vs. 43%, AOR 3.8, $p < 0.01$) and non-fibrotic forms (88% vs. 51%, AOR 5.75, $p < 0.01$), with an overall diagnostic sample rate of 78% for TBCB vs. 48% for TBFB (AOR 4.24, $p < 0.01$). TBCB was associated with a higher risk of significant bleeding (10% vs. 3%, $p < 0.01$), while the incidence of pneumothorax was similar (11% vs. 9%) [72].

A large retrospective cohort of 699 patients who underwent TBCB for diffuse parenchymal lung diseases confirmed the good clinical tolerability of the procedure, reporting a pneumothorax rate of 19.2%, severe bleeding in 0.7%, and 30-day mortality of 0.4%, suggesting an acceptable safety profile in centers equipped with proper complication management protocols [4].

Another study comparing cryobiopsy with surgical biopsy showed a significantly more favorable safety profile for TBCB: procedure-related mortality was 0.3% for TBCB versus 2.7% for SLB, with a shorter median hospital stay (2.6 days vs. 6.1 days) and no cases of major bleeding, although pneumothorax occurred in 20.2% of patients [29]. However, a prospective study by Romagnoli et al. reported poor diagnostic concordance between TBCB and SLB, with histological agreement in only 38% of cases ($\kappa = 0.22$) and multidisciplinary diagnostic agreement (MDA2) of 48% for TBCB versus 62% for SLB, indicating that in over half of the patients (52%), TBCB alone would have led to a different therapeutic decision, confirming the irreplaceable role of surgical biopsy in complex, unclassifiable ILD cases [71].

In a prospective multicenter clinical study conducted across 10 hospitals, TBCB was directly compared to conventional TBLB in the same ILD patients. TBCB showed a significantly higher diagnostic yield (47.6% vs. 19.4%; $p < 0.0001$), though associated with a higher rate of moderate bleeding (6.5% vs. 0.8%), emphasizing the need for preventive measures such as orotracheal intubation and use of occlusion balloons to ensure procedural safety [32].

Consistent with these data, an updated systematic review for the ATS/ERS/JRS/ALAT guidelines concluded that TBCB is a relatively safe procedure, with mild to moderate bleeding in 30% of cases, pneumothorax in 8%, and negligible rates of severe complications. Furthermore, it is associated with significantly shorter hospital stays compared to SLB/VATS, reducing patient burden and healthcare costs [28]. These findings suggest that even fragile populations—such as pediatric patients, the elderly, and individuals with comorbidities—who were historically excluded from invasive biopsy procedures due to high risk, may benefit from cryobiopsy, which often represents the only viable option for obtaining diagnostic tissue [68–69].

The 2022 joint ATS/ERS/JRS/ALAT guidelines on idiopathic pulmonary fibrosis (IPF) issued a conditional recommendation in favor of TBCB, acknowledging its utility in bronchoscopy-experienced centers with integrated multidisciplinary diagnostic teams [27].

At the same time, efforts are underway to standardize the technique—a critical step to ensure reproducibility and minimize complications. Key technical parameters to harmonize include the number of biopsies, freezing duration, cryoprobe diameter, and the use of bleeding control devices such as Fogarty balloons [2]. The use of fluoroscopy or EBUS guidance is also strongly recommended to enhance sampling precision.

Another crucial factor for the safe and effective implementation of TBCB is operator training. Although no standardized international training program currently exists, there is broad consensus on the need for structured and dedicated educational pathways to ensure proper and safe execution of the procedure.

5. Cryobiopsy in the modern management of NSCLC and molecular oncology

In modern oncology, particularly in the management of non-small cell lung cancer (NSCLC), obtaining an adequate tissue sample is a critical step for ensuring accurate diagnosis, precise histopathological classification, and comprehensive molecular profiling. These components are fundamental for selecting targeted therapies and immunotherapies, which constitute the cornerstones of precision medicine.

Specifically, the identification of genetic alterations (e.g., EGFR, ALK, ROS1) and the assessment of biomarkers such as PD-L1 require tissue samples with sufficient quality and quantity of DNA, RNA, and proteins. In this context, cryobiopsy is emerging as an innovative technique, showing particular promise in the clinical management of patients with NSCLC.

In a prospective clinical study involving 121 patients with suspected or confirmed lung cancer, transbronchial cryobiopsy yielded significantly more suitable samples for molecular analysis than conventional forceps biopsy, with higher quantities of extracted DNA (median: 1.60 µg vs. 0.58 µg; $P = 0.02$) and RNA (median: 0.62 µg vs. 0.17 µg; $P < 0.01$), and a greater proportion of samples with PD-L1 expression >1% (51% vs. 42%). Moreover, TBCB provided superior morphological diagnostic capacity, with a significantly higher rate of definitive histomorphological diagnoses (86% vs. 74%, $P < 0.01$) [33].

A retrospective study of 414 NSCLC patients showed that bronchoscopic cryobiopsy enabled a significantly higher detection rate of EGFR activating mutations compared to other tissue sampling techniques, identifying 29 mutations in 125 patients (21.6%) versus 42 mutations in 298 patients (13.8%) using conventional techniques ($p < 0.05$). This advantage was particularly evident in central tumors (19.6% vs. 6.5%, $p < 0.05$) and also favorable in peripheral tumors (33.3% vs. 26.9%), suggesting that cryobiopsy may enhance the molecular stratification of patients eligible for personalized targeted therapies [34].

As previously mentioned, cryobiopsy has also demonstrated reliability in assessing PD-L1 expression, with high concordance rates compared to surgical samples, especially in cases with high PD-L1 levels (≥50%).

In a prospective study of 16 lung cancer patients, the proportion of patients with PD-L1 ≥50% was higher with TBCB (18.8%) than with TBB (12.5%), as was PD-L1 ≥1% (56.3% vs. 37.5%). For the ≥50% threshold, TBCB sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), concordance, and kappa coefficient were 66.7%, 100%, 100%, 92.9%, 93.8%, and 0.76, respectively. For the ≥1% threshold, the values were lower: sensitivity 44.4%, specificity 71.4%, PPV 66.7%, NPV 50%, concordance 56.3%, and kappa 0.15. These findings suggest that cryobiopsy is more reliable in detecting high PD-L1 expression, a key parameter for selecting patients for first-line pembrolizumab immunotherapy [15].

The high histological quality of samples obtained by TBCB may also play a critical role in epigenetic research, particularly for DNA methylation analysis. Recent studies have shown that aberrant methylation profiles identified in bronchial biopsies are emerging as innovative tools for the early detection of lung cancer, through epigenetic signatures capable of distinguishing tumor tissue from normal tissue. In this setting, the high DNA integrity and larger tissue volume provided by TBCB—compared to conventional biopsies—make it particularly suitable for advanced molecular investigations, including methylation profiling with prognostic relevance. This is especially important in stage I NSCLC, where methylation of genes such as HIST1H4F, PCDHGB6, NPBWR1, ALX1, and HOXA9 has been associated with an increased risk of recurrence (HR 3.24; $p = 0.001$), potentially guiding patient selection for adjuvant chemotherapy [37].

Samples obtained via cryoprobe in a retrospective study of 40 NSCLC patients who underwent both cryobiopsy and conventional biopsy at the same site also demonstrated high reliability for immunohistochemistry (IHC) analysis—not only for PD-L1, which showed 85% concordance ($\kappa = 0.835$), but also for HER2 (72.5% concordance, $\kappa = 0.637$) and HER3 (75% concordance, $\kappa = 0.697$). These findings indicate that the freeze-thaw cycle inherent to cryobiopsy does not compromise IHC quality, further supporting its suitability for precision oncology [38].

In conclusion, transbronchial cryobiopsy represents a highly promising and increasingly established technique in the management of NSCLC, particularly within the framework of precision medicine. The superior histological quality of the samples, the higher yield and integrity of extracted DNA and RNA, and the high reliability in IHC and biomarker analyses—such as PD-L1, EGFR, ALK, ROS1, and epigenetic alterations—make this biopsy technique an ideal tool for advanced molecular profiling. Furthermore, the ability to obtain sufficient material from a single biopsy for both histological and molecular diagnosis reduces the need for repeated sampling and shortens diagnostic timelines, with important clinical implications for treatment selection. The integration of TBCB into NSCLC diagnostic pathways thus represents a critical step toward increasingly personalized and biologically driven lung cancer treatment.

Table 1 illustrates the applicability of tissues obtained through transbronchial cryobiopsy to genomic, transcriptomic, epigenetic, and immunohistochemical analyses.

6. Transbronchial Cryobiopsy in IPF: a key tool for diagnosis, early molecular stratification, and integrated exploration of pathogenetic mechanisms through multi-omic approaches

Idiopathic pulmonary fibrosis (IPF) represents one of the most complex challenges in the field of interstitial lung diseases (ILDs), due to its significant clinical heterogeneity, unpredictable progression, and lack of reliable biomarkers for early diagnosis, effective prognostic stratification, and appropriate therapeutic selection. In this context, molecular characterization of the disease—through the identification of epigenetic, transcriptomic, and proteomic markers—has become a strategic priority in precision medicine. Among the emerging clinical applications of transcriptomic technologies, the Envisia Genomic Classifier has proven to be a useful tool in supporting the diagnosis of IPF, particularly in patients with ILD presenting indeterminate radiological patterns. This test, based on the expression of 190 genes, is capable of identifying a molecular signature consistent with the usual interstitial pneumonia (UIP) pattern with high specificity, approximately 90%. In patients testing positive, a definitive IPF diagnosis was confirmed in 78.6% of cases, with a significant impact on clinical management, which was altered in over 60% of situations [40].

Furthermore, a large-scale decision-impact study demonstrated that integrating the Genomic Classifier into clinical practice significantly increased IPF diagnoses (from 30% to 69%, OR 16.43; $p < 0.001$), improved diagnostic confidence (≥90%), and led to greater use of antifibrotic therapy (from 12% to 50%, OR 8.22; $p < 0.001$), while simultaneously reducing the need for surgical lung biopsy (SLB) (from 26% to 17%, OR 0.49; $p = 0.03$). However, for the Envisia test to reach its full diagnostic potential, it must be applied to high-quality biopsy samples. The effectiveness of this transcriptomic tool depends on the availability of sufficient, intact RNA—something not reliably obtainable with conventional forceps transbronchial biopsy, but well supported by transbronchial cryobiopsy (TBCB). Without TBCB, the clinical applicability of the Genomic Classifier would be severely limited, both in terms of analytical reliability and clinical utility. Therefore, TBCB emerges not only as an alternative morphological sampling technique to surgery but also as a technical prerequisite for the effective and reproducible implementation of advanced molecular tests such as Envisia.

In addition to its clinical application for diagnosis and patient stratification, the quality of the biopsy sample is also crucial in translational research, particularly in studying pathogenetic mechanisms and identifying prognostic biomarkers in IPF. In this setting, TBCB—due to its ability to yield morphologically and molecularly preserved tissue—has proven essential for enabling high-throughput molecular analyses. Among the most promising emerging biomarkers in IPF research are microRNAs (miRNAs), small non-coding regulators involved in fibrogenesis. Approximately 10% of miRNAs are significantly dysregulated in fibrotic lung tissue; for instance, miR-21 is frequently overexpressed and promotes fibroblast activation, while antifibrotic miRNA families—including let-7, miR-29, miR-30, and the miR-17~92 cluster—are markedly downregulated. These miRNAs negatively regulate the TGF-β1 signaling pathway, contributing to the perpetuation of fibrotic pathogenetic circuits. Direct analysis of these profiles in TBCB-derived samples has demonstrated their value as both diagnostic biomarkers and potential therapeutic targets [35,36].

Beyond transcriptomics, integrated proteomic profiling of tissue and plasma has also identified fibrosis-associated signatures, such as increased levels of profibrotic chemokines (e.g., CCL17 and CCL22) and reduced collagen fragments, with potential prognostic and predictive significance [39]. Recent studies suggest that these chemokines are not merely markers but active players in the pathogenesis of IPF. Specifically, elevated CCL22 and CCL17 levels detected in bronchoalveolar lavage fluid (BAL) from IPF patients—compared to healthy subjects and those with CTD-ILD—were associated with CCR4-positive alveolar macrophages. Immunohistochemical analysis confirmed the localization of CCL22 in CD68-positive macrophages and CCL17 in hyperplastic epithelial cells, suggesting selective interactions with immune subpopulations involved in fibrotic progression. Additionally, an inverse correlation between CCL22 and DLCO/VA supports its direct involvement in respiratory impairment [39].

In conclusion, the high quality of biopsy tissue obtained via TBCB is not only essential for the histological diagnosis of IPF but also for advancing pathogenetic research and identifying novel prognostic and therapeutic biomarkers.

Transbronchial cryobiopsy is also gaining a central role in epigenomic studies, especially for DNA methylation analysis in complex diseases such as pulmonary fibrosis and lung cancer. In IPF, 738 differentially methylated CpG regions have been identified compared to controls, including hypermethylation of antifibrotic genes such as Thy-1, PTGER2, CDKN2B, COX-2, c8orf4, and p14ARF, and hypomethylation of DNA repair genes such as MGMT, indicating profound disruption of epigenetic homeostasis. In parallel, numerous hypermethylated tumor suppressor genes have been identified in lung cancer—including SOX17, APC, RAR-β, RASSF1A, HOXA9, PITX1, and SMAD3—also detectable in biological fluids (BALF, plasma), with diagnostic sensitivity reaching up to 90% in some panels. These findings confirm that DNA methylation is not only a shared pathogenetic mechanism between IPF and lung cancer but also a potentially actionable biomarker in molecular diagnostics via cryobiopsy [42].

Cryobiopsy has demonstrated the clinical feasibility of integrating single-cell RNA sequencing (scRNA-seq) using bronchoscopy-obtained tissue, allowing early molecular stratification through the subtyping of fibrotic cellular niches in ILD [41]. scRNA-seq is an advanced sequencing technology that enables gene expression analysis at the single-cell level, allowing identification of distinct cell subpopulations and functional dynamics within heterogeneous tissues.

In IPF, this technology revealed at least 13 distinct cell populations, including macrophages, alveolar epithelial cells (AT1 and AT2), endothelial cells, and T, B, and NK lymphocytes [41]. Among these, a unique profibrotic alveolar macrophage subpopulation derived from monocytes was identified, enriched in key genes such as SPP1, CHI3L1, MMP9, MARCKS, and IL1RN, coexisting with homeostatic resident macrophages expressing PPARG and MRC1. In type II epithelial cells, a fibrosis-specific subpopulation (cluster 3) was characterized by high expression of DMBT1, SERPINA1, CHI3L1, and senescence markers, supported by a significantly elevated senescence transcriptomic score ($p = 0.0001$). A non-overlapping Wnt signaling pattern was also observed,

with WNT7B and AXIN2 expressed in distinct epithelial subtypes, as confirmed by in situ RNA hybridization. The detection of rare lymphatic vascular progenitor cells expressing PROX1, MMRN1, and TBX1 in TBCB samples further underscores the value of this technique in exploring specific cellular niches and understanding the pathogenetic mechanisms of pulmonary fibrosis.

In summary, transbronchial cryobiopsy (TBCB) serves as an enabling tool for precision medicine in IPF by providing high-quality tissue samples suitable for advanced multi-omic analyses. Integration with technologies such as the Envisia Genomic Classifier and single-cell RNA sequencing has improved diagnostic accuracy, enabled the identification of fibrotic cell subtypes, and supported early molecular stratification strategies. Furthermore, TBCB has facilitated the investigation of epigenetic, transcriptomic, and proteomic biomarkers associated with disease progression and prognosis, offering new avenues for the development of personalized, targeted therapies.

7. Radiomics and TBCB: Integration with HRCT Imaging, Radio-Molecular Correlations, and Predictive Models in ILD and Thoracic Cancer

Radiomics is an emerging and innovative approach that enables the quantitative extraction of a large number of features from medical imaging, particularly high-resolution computed tomography (HRCT). It offers new non-invasive biomarkers useful for diagnosis, risk stratification, and monitoring of lung diseases [43]. In the context of interstitial lung diseases (ILDs), radiomics has demonstrated notable effectiveness, especially when integrated with transbronchial lung cryobiopsy (TBCB), within a combined diagnostic model that enhances both quantitative imaging and tissue analysis.

HRCT remains the primary imaging tool in the evaluation of fibrosing ILDs, not only to identify suggestive radiologic patterns but also to precisely guide biopsy sampling [46][47]. When the radiologic pattern is not specific enough for a definitive diagnosis, detailed image analysis allows for the selection of representative pulmonary regions, avoiding consolidated fibrotic areas or honeycombing in favor of intermediate patterns or signs of active inflammation [48]. This targeted sampling strategy significantly improves the diagnostic yield of TBCB, reducing the risk of non-informative tissue and enhancing the correlation between histologic and radiologic features.

The integration of radiomics into this diagnostic pathway enables a quantitative and objective interpretation of HRCT images, facilitating correlations between radiologic data and molecular or histopathologic findings from biopsies. In a prospective study of 100 patients with fibrosing ILD, over 1,600 radiomic features were extracted from each CT image to develop predictive models of cellular infiltration in fibrotic tissue. These models showed excellent performance both quantitatively (RMSE = 0.797) and for classification (accuracy 70%, F1-score 0.73), confirming the clinical potential of radiomics as a non-invasive biomarker of inflammatory activity [49].

Other studies have demonstrated the ability of radiomics to distinguish healthy lung tissue from fibrotic regions, and to differentiate typical from atypical UIP patterns, with very high diagnostic accuracy. A radiomics model based on HRCT combined with a Random Forest algorithm achieved an AUC of 1.0 for distinguishing normal from fibrotic lungs, 0.96 for differentiating IPF/UIP from non-IPF ILDs, and 0.66 for distinguishing radiologically or histologically confirmed IPF from non-IPF ILDs, suggesting that radiomics applied to HRCT may represent a highly accurate and non-invasive diagnostic tool, potentially reducing the need for surgical biopsy [45].

A promising development is the integration of in vivo cellular imaging via probe-based confocal laser endomicroscopy (pCLE) with radiomics. While pCLE enables real-time visualization of alveolar structures during bronchoscopy—optimizing biopsy site selection and improving safety and diagnostic accuracy—radiomics can guide bronchoscopists toward lung regions with the highest predictive value, further enhancing TBCB performance. A study of 17 ILD patients showed that combining TBLC with pCLE enabled in vivo identification of fibrotic areas, blood vessels, and pleura, with good correlation to histological findings, suggesting a potential alternative to conventional fluoroscopy [pCLE study].

The synergy between radiomics and TBCB has also been applied to the development of complex predictive models combining imaging data, histopathologic findings, and serum biomarkers. In a study of patients with rheumatoid arthritis-associated ILD (RA-ILD), a multivariate model integrating HRCT radiomic features with plasma levels of the biomarker KL-6 achieved an AUC of 0.94 for risk stratification. Another retrospective study of 177 patients led to the development of a predictive nomogram combining 19 radiomic features with clinical variables, including the ILD-GAP score, achieving AUCs of 0.948 in the training cohort and 0.923 in the validation cohort, demonstrating excellent calibration and clinical utility [51].

Radiomics and TBCB integration is also proving highly promising in thoracic oncology. Radiomic techniques applied to chest CT are already used to characterize pulmonary nodules, differentiate benign from malignant lesions, and non-invasively identify histologic subtypes and driver mutations. In a study of 161 NSCLC patients, a radiogenomic model using the XGBoost algorithm achieved AUCs of 0.89 for EGFR and 0.81 for KRAS mutations, with specificity over 88% and accuracy above 83%, even in imbalanced cohorts. These results were reinforced by data balancing algorithms and SHAP analysis, which identified key predictive features [52].

In this setting, TBCB plays a complementary and fundamental role by enabling histologic confirmation of suspicious lesions and providing adequate tissue for molecular profiling, even in frail patients. Integration of histopathologic and genomic data obtained from TBCB with radiomic parameters strengthens the validity of predictive models and supports a more personalized approach to precision medicine. Radiomics can also be used to identify the most aggressive areas within a heterogeneous nodule, guiding targeted biopsy and increasing the likelihood of obtaining molecularly relevant material.

Ultimately, combining radiomics with TBCB creates a virtuous diagnostic cycle: advanced imaging guides targeted sampling, while molecular and histologic analyses validate and refine radiomic parameters, contributing to the development of increasingly accurate diagnostic and prognostic tools for ILD and lung cancer, and facilitating the transition to truly personalized medicine.

8. Artificial Intelligence in Histologic Analysis of Cryobiopsies: Morphologic Automation, Multimodal Integration, and Support for ILD and Lung Cancer Classification

The integration of artificial intelligence (AI) in the histopathologic analysis of lung cryobiopsy samples represents a true revolution in respiratory diagnostics. The use of digital pathology allows for high-resolution scanning of histologic slides, enabling the application of deep learning algorithms for the automated recognition of complex morphologic patterns. These algorithms demonstrate diagnostic accuracy comparable to, and in some cases exceeding, that of expert pathologists.

A notable example is the CAMELYON16 study, in which a deep learning model applied to whole-slide digital images achieved an impressive AUC of 0.994 in identifying lymph node metastases in breast cancer—significantly outperforming pathologists under routine conditions (average AUC 0.810) and approaching that of an expert pathologist working without time constraints (AUC 0.966) [55]. Similarly, another study developed an AI system capable of analyzing thousands of digitized histopathology images without manual annotations, using only general clinical diagnoses for training. The system achieved outstanding results, with AUCs above 0.98 for various cancers such as prostate carcinoma, basal cell carcinoma, and lymph node metastases of breast cancer. It automatically flagged suspicious cases and excluded up to 75% of slides from further review—without missing any positive cases, thanks to 100% sensitivity [56].

This approach demonstrates how AI can make diagnostics more efficient and scalable, significantly reducing pathologists' workloads. In ILDs—where diagnostic complexity is high due to morphologic overlap between subtypes (e.g., UIP)—AI has proven extremely useful. A system called MIXTURE has assisted pathologists in identifying key microscopic features such as dense fibrosis, fibroblastic foci, and lymphocytic infiltrates. It achieved an AUC of 0.90 in the validation group, aiding in the differential diagnosis of UIP, a condition with severe prognosis [57].

In IPF, AI has enabled the identification of prognostic biomarkers that are difficult to assess manually. A convolutional neural network (CNN) applied to IPF samples showed that fibroblastic foci (FF) were significantly associated with poor prognosis, while increased interstitial mononuclear inflammation and intra-alveolar macrophages correlated with better survival [58].

Another major advancement is the integration of clinical, molecular, radiologic, and histologic data. Analysis of lung cryobiopsies combined with RNA-Seq led to the identification of key biomarkers for IPF. Machine learning models applied to clinical and histologic data identified genes such as FHL2, HPCAL1, RNF182, and SLAIN1 with excellent diagnostic accuracy (AUC up to 1.00) and potential pathogenetic roles in fibrosis [64].

Multimodal integration of clinical, radiologic, and histologic data may soon provide decisive diagnostic support in ILDs, such as differentiating idiopathic UIP from chronic hypersensitivity pneumonitis. Recent case studies have shown that deep learning models can directly identify morphologic patterns—such as granulomas and other microscopic lesions—from digital slides, improving diagnostic sensitivity [66].

Finally, the application of AI to TBCB samples is also yielding promising results in thoracic oncology. AI-based models trained on digital slides from cryobiopsies have enabled accurate classification of NSCLC histotypes, achieving diagnostic accuracy comparable to expert pathologists. This approach also supports early identification of predictive biomarkers, making AI a key tool in histopathologic analysis for thoracic oncology and pulmonary diseases [67].

In conclusion, the adoption of artificial intelligence in interpreting lung cryobiopsies represents a fundamental step in the evolution of respiratory diagnostics. However, it is essential that the biological samples provided to AI systems are intact and of optimal quality. Sample quality is critical to ensure that deep learning algorithms can extract accurate and relevant information from histologic data, without interference from artifacts or sampling defects. In this context, cryobiopsy plays a central role, allowing the collection of high-quality pulmonary tissue samples while preserving lesion structure and morphology.

Table 2 illustrates the complementary and synergistic roles of emerging technologies in data-driven precision respiratory medicine.

9. Conclusions

Transbronchial lung cryobiopsy (TBCB) has progressively established itself as a key technology in advanced thoracic diagnostics, offering an effective balance between diagnostic accuracy, safety, and compatibility with the demands of modern medicine. Unlike traditional biopsy techniques, TBCB enables the collection of large, well-preserved, and structurally intact tissue samples with minimal invasiveness. This makes it particularly suitable not only for conventional histopathological analysis but also for the application of advanced molecular techniques, such as next-generation sequencing (NGS), transcriptomic, epigenomic, and proteomic profiling.

From a clinical perspective, TBCB has demonstrated a significant impact on the diagnosis of ILDs, improving the identification of histological patterns and playing a decisive role in multidisciplinary team discussions, which represent the cornerstone of managing these complex conditions. In thoracic oncology, cryobiopsy has shown enormous potential in providing adequately representative samples for comprehensive molecular tumor profiling, including extended genomic analysis, tumor mutational burden assessment, complex transcriptional signatures, and PD-L1 expression.

The architectural integrity of tissue obtained through cryobiopsy results in higher quantity and quality of extractable DNA/RNA, facilitating the success of high-complexity molecular analyses and reducing the need for repeat procedures.

One of the most promising future directions is the integration of TBCB with emerging technologies such as radiomics and artificial intelligence (AI). The extraction of quantitative data from HRCT images and the automated analysis of digitized histological slides, supported by machine learning and deep learning models, are enabling the development of sophisticated predictive tools capable of correlating radiologic, histologic, and molecular patterns. Within this framework, this innovative biopsy procedure provides the essential tissue for validating radiomic data and feeding AI algorithms with high-quality biological information, thereby making diagnosis increasingly precise, reproducible, and personalized.

Equally important is the expansion of TBCB indications to previously underserved populations, such as pediatric patients, the elderly, and individuals with significant comorbidities—groups historically excluded from invasive surgical procedures.

The future of TBCB lies in its systemic integration with digital platforms, intelligent algorithms, omics sciences, and personalized clinical pathways. To fully realize this potential, however, it will be essential to invest in specialist training, the standardization of procedural protocols, the optimization of complication prevention strategies, and the dissemination of technical expertise across a growing number of respiratory centers.

Table 3 outlines the technological, clinical, and methodological development perspectives necessary for consolidating TBCB in advanced respiratory diagnostics.

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