14. Terragni P, Mascia L, Fanelli V, Biondi-Zoccai G, Ranieri VM. Accuracy of esophageal pressure to assess transpulmonary pressure during mechanical ventilation. *Intensive Care Med* 2017;43:142–143.
15. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. *Am J Respir Crit Care Med* 2014; 190:252–257.
16. Milic-Emili J. Is weaning an art or a science? *Am Rev Respir Dis* 1986; 134:1107–1108.
17. Lennon J, McCartney P. The long and winding road. 1970.

Endobronchial Optical Coherence Tomography for the Diagnosis of Fibrotic Interstitial Lung Disease

A Light at the End of the Tunnel?

An accurate diagnosis of fibrotic interstitial lung disease (ILD) is critical to inform prognostication and selection of pharmacotherapy. Clinicians are ideally able to integrate the clinical history, laboratory findings, and morphologic features on chest imaging within multidisciplinary discussion (MDD) to achieve a consensus diagnosis. However, despite this process, a confident diagnosis remains elusive in approximately 15% of patients (1), and there is often a need for additional information to guide management decisions. This diagnostic uncertainty has traditionally prompted consideration of histopathologic evaluation via surgical lung biopsy (SLB), but this procedure is associated with substantial risk of morbidity and mortality (2).

Several novel diagnostic techniques have recently been studied in an attempt to overcome the risks of SLB. For example, transbronchial lung cryobiopsy has a superior safety profile that permits an expanded role in ILD (3, 4), although this procedure still suffers from issues of high interobserver variability and some challenges in implementation (5). More recently, a genomic classifier has emerged as an additional diagnostic tool that reduces the subjectivity commonly associated with interpretation of histopathology; however, this tool still requires tissue sampling and has uncertain utility beyond distinguishing usual interstitial pneumonia (UIP) from non-UIP patterns (6, 7).

Optical coherence tomography (OCT) is the latest addition to this growing list of bronchoscopic tools potentially useful in the diagnosis of ILD, offering a minimally invasive method of high-resolution imaging of the lung parenchyma that avoids the major complications of SLB. Endobronchial OCT employs near-infrared light to visualize surrounding structures with a resolution of <10 μm, approaching the 2-μm resolution of microscopy. Analogous to radial ultrasound, an OCT probe is passed through the working channel of a bronchoscope, generating light that passes through and interacts with circumferent tissue. The resultant backscatter is detected and used to create a cross-sectional image 8 mm in diameter, with subsequent pullback of the probe producing a three-dimensional reconstruction of sequential images along the path of the selected airway. OCT has been used to assess smooth muscle and airway wall thickness in asthma after bronchial thermoplasty (8, 9), to distinguish early from invasive carcinoma (10), and to identify major cancer subtypes (11, 12).

In this issue of the *Journal*, the report by Nandy and colleagues (pp. 1164–1179) serves as a proof-of-concept study comparing the ability of OCT to distinguish UIP from non-UIP patterns, using SLB as the histopathological gold standard (13). This builds on previous work from the same group that first reported successful use of OCT *in vivo* to identify a UIP pattern in five patients with idiopathic pulmonary fibrosis (14). Impressively, the current study showed sensitivity and specificity of 100% in detecting a UIP pattern, suggesting OCT may have a significant role in the evaluation of fibrotic ILD, potentially relieving much of the historical reliance on SLB.

These are very encouraging findings, but substantial additional work is needed before widespread clinical implementation of this technique (Figure 1). Most importantly, external validation across multiple centers and diverse populations is critical to safeguard against the damage that can arise from ILD misclassification. In addition, larger studies should also evaluate interobserver variability in interpretation and the potential of OCT to identify more specific histopathologic patterns beyond simply separating UIP and non-UIP patterns. These future studies should further evaluate the impact of OCT on clinical diagnosis and diagnostic confidence when employed in the real-world scenario of an MDD. Finally, the clinical impact of OCT in fibrotic ILD should then be assessed, including how its use affects meaningful outcomes such as time to diagnosis and selection of pharmacotherapy.

After the validation of OCT as a reliable diagnostic tool, it will be necessary to optimize its operationalization in a variety of settings. As an advanced imaging technique currently used predominantly as a research tool, successful uptake requires conceptual acceptance of its clinical utility, widespread access to the necessary equipment, and adequate training of both proceduralists and pathologists. Given the impracticality of real-time quality control by an experienced pathologist, proceduralists must achieve competence with OCT to ensure adequate image acquisition during bronchoscopy. This includes selecting imaging locations at multiple anatomic sites, confirming the subpleural location of the OCT catheter before scanning, assessing image quality in real time, and

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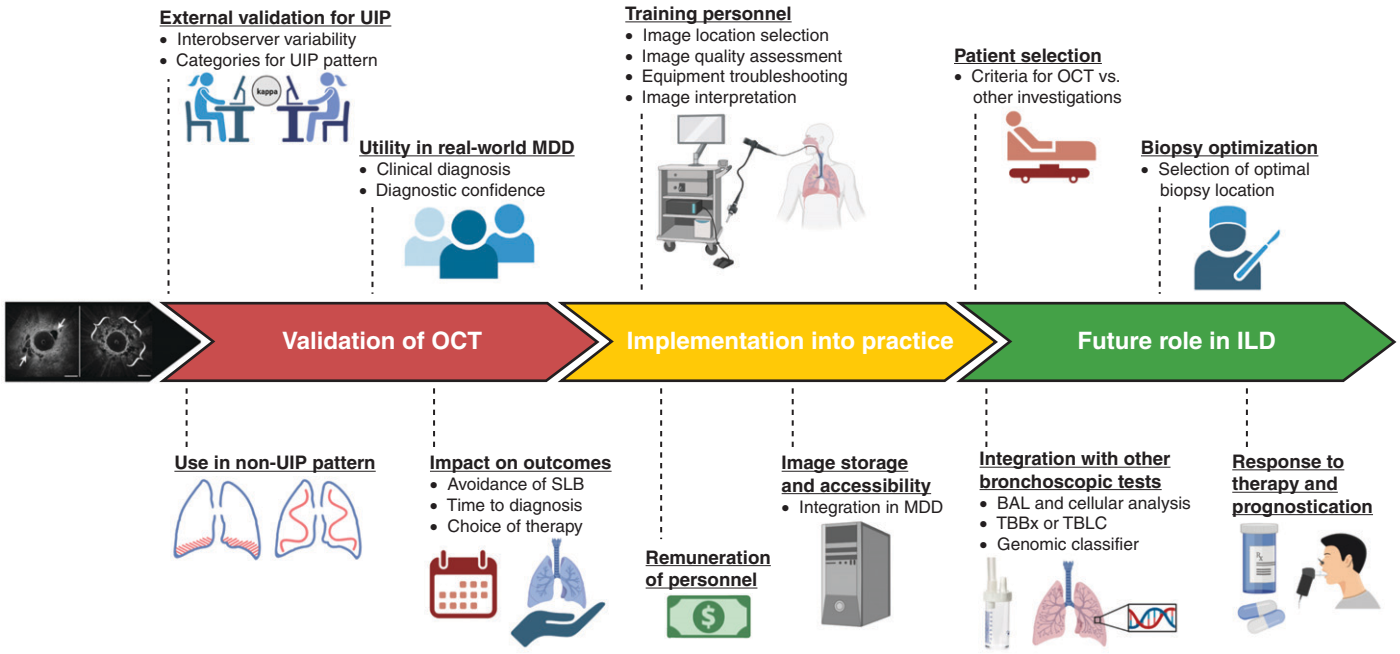

Figure 1. Roadmap highlighting additional work required to further investigate and implement endobronchial OCT as a new technique for the evaluation of patients with fibrotic ILD (created with BioRender.com). The OCT image is modified and reprinted with permission by Reference 14. ILD = interstitial lung disease; MDD = multidisciplinary discussion; OCT = optical coherence tomography; SLB = surgical lung biopsy; TBBx = transbronchial biopsy; TBLC = transbronchial lung cryobiopsy; UIP = usual interstitial pneumonia.

troubleshooting equipment failures. Similarly, pathologists must be trained to interpret and report OCT findings in a standardized manner, including integration and synthesis of data from multiple anatomic sites, ideally with the support of clinical practice guidelines. Furthermore, the development of remuneration standards for OCT will ensure clinicians are not dissuaded from performing this technique when indicated and that physicians are properly compensated for their time and effort. Finally, additional logistics will need to be considered, including the costs of equipment and its maintenance, how images will be captured and stored, and how to seamlessly integrate this information in an MDD.

After validation and paralleling its implementation into clinical practice, the role of OCT in the overall approach to ILD diagnosis will need to be determined. For example, further work would be needed to identify selection criteria for patients most appropriate for this new tool. OCT could also be integrated with other bronchoscopic techniques to create a panel of complementary tests that maximize diagnostic performance, including BAL fluid cellular analysis and a recently studied genomic classifier. In cases in which SLB is still necessary, OCT might help identify optimal biopsy locations to minimize sampling error. Finally, beyond its purely diagnostic role, OCT could be able to discriminate between fibrotic and cellular patterns of disease, informing both response to pharmacotherapy and prognosis.

Although there remains much to do, the current study represents a major step forward for OCT in fibrotic ILD, hinting at its potential as a much-needed minimally invasive tool in the diagnosis of a heterogeneous and challenging disease. Despite these promising preliminary results and exciting possible applications, additional robust data are needed to better understand the utility and limitations of OCT before widespread clinical implementation. The encouraging data presented by Nandy and colleagues provide justification for these much-needed future studies that will hopefully lead to a safer and more accurate approach to ILD diagnosis. ■

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References

1. Guler SA, Ellison K, Algamdi M, Collard HR, Ryerson CJ. Heterogeneity in unclassifiable interstitial lung disease. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2018;15:854–863.
2. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med* 2016;193:1161–1167.
3. Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, *et al.* Poor concordance between sequential transbronchial lung

cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases. *Am J Respir Crit Care Med* 2019;199: 1249–1256.
4. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, *et al.*; Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance (COLDICE) Investigators. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020;8:171–181.
5. Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease. A systematic review and metaanalysis. *Ann Am Thorac Soc* 2016;13:1828–1838.
6. Raghu G, Flaherty KR, Lederer DJ, Lynch DA, Colby TV, Myers JL, *et al.* Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study. *Lancet Respir Med* 2019;7:487–496.
7. Richeldi L, Scholand MB, Lynch DA, Colby TV, Myers JL, Groshong SD, *et al.* Utility of a molecular classifier as a complement to high-resolution computed tomography to identify usual interstitial pneumonia. *Am J Respir Crit Care Med* 2021;203:211–220.
8. Adams DC, Hariri LP, Miller AJ, Wang Y, Cho JL, Villiger M, *et al.* Birefringence microscopy platform for assessing airway smooth muscle structure and function in vivo. *Sci Transl Med* 2016;8: 359ra131.
9. Kirby M, Ohtani K, Lopez Lisbona RM, Lee AM, Zhang W, Lane P, *et al.* Bronchial thermoplasty in asthma: 2-year follow-up using optical coherence tomography. *Eur Respir J* 2015;46:859–862.
10. Lam S, Standish B, Baldwin C, McWilliams A, leRiche J, Gazdar A, *et al.* In vivo optical coherence tomography imaging of preinvasive bronchial lesions. Clin Cancer Res 2008;14:2006–2011.
11. Hariri LP, Mino-Kenudson M, Lanuti M, Miller AJ, Mark EJ, Suter MJ. Diagnosing lung carcinomas with optical coherence tomography. *Ann Am Thorac Soc* 2015;12:193–201.
12. Hariri LP, Applegate MB, Mino-Kenudson M, Mark EJ, Medoff BD, Luster AD, *et al.* Volumetric optical frequency domain imaging of pulmonary pathology with precise correlation to histopathology. *Chest* 2013; 143:64–74.
13. Nandy S, Raphaely RA, Muniappan A, Shih A, Roop BW, Sharma A, *et al.* Diagnostic accuracy of endobronchial optical coherence tomography for the microscopic diagnosis of usual interstitial pneumonia. *Am J Respir Crit Care Med* 2021;204:1164–1179.
14. Hariri LP, Adams DC, Wain JC, Lanuti M, Muniappan A, Sharma A, *et al.* Endobronchial optical coherence tomography for low-risk microscopic assessment and diagnosis of idiopathic pulmonary fibrosis in vivo. *Am J Respir Crit Care Med* 2018;197:949–952.

In Case of Invasive Nodule, Break Ground Glass

After decades of stagnation, lung cancer survival is trending upward with numerous reports of long-term survival in patients with advanced lung adenocarcinoma (LUAD) treated with targeted therapeutics and of overall 5-year survival rates exceeding 20% (1). Much of the improvement is attributed to the introduction of genomic biomarker–based targeted therapeutics in advanced disease, starting after the approval of EGFR (epidermal growth factor receptor) tyrosine kinase receptor therapy for first-line treatment of EGFR-mutated lung cancer in 2013 (2). Trends in advanced disease survival are expected to continue with the standard use of immunotherapy and with ongoing development of drugs targeted to drivers and to the immune response.

Appropriately, attention is being directed toward repurposing these approaches to early-stage disease, with notable benefits demonstrated by adjuvant use of osimertinib in resected early-stage EGFR-mutant lung adenocarcinoma (3) and by neoadjuvant immunotherapy trials in early-stage lung cancer (4). These advances are welcome because the 5-year survival for early-stage lung cancer is 60%, which is lower than the *overall* 5-year survival rates for breast and prostate cancer.

Importantly, there are subtypes of early-stage lung adenocarcinoma that routinely have survival rates of 95–100% after resection (5). Advances in the clinical, pathological, and biological understanding of these tumors contributed to the updated International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma that featured identification of pathological subtypes of adenocarcinoma *in situ*, minimally invasive carcinoma, and lepidic predominant carcinoma, that are composed entirely of or in part by a noninvasive lepidic morphology component that is correlated with a ground-glass opacity radiographic pattern on computed tomography (CT) imaging (6). The 5-year survival rates after resection of these lepidic-containing tumors is high and is associated with the pathological extent of invasion and with the morphological subtype of the invasive solid component (7).

Reassured by the experience accumulated from managing patients with early-stage lung adenocarcinoma tumors detected incidentally or through lung cancer screening programs, guidance has been developed that suggests that "active surveillance" with follow-up chest CT imaging is an appropriate strategy for selected patients with chest imaging findings of lung nodules with a ground-glass component that is purely nonsolid or part-solid (8, 9). Cohort studies such as the Early Lung Cancer Action Program consortium have reported 100% lung cancer survival rates following a surveillance strategy for nonsolid and part-solid lesions (10).

In this issue of the *Journal*, Chen and colleagues (pp. 1180–1191) address the important question as to whether chest CT–detected nodules with a ground-glass component mirror the biology and genomics of resected tumors with a lepidic component (11). In a prospective study of 101 patients with lung cancer, 31 had nodules

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