Pulmonary Pathology Journal Club
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1. Analytical and clinical validation of the Oncomine Dx Target Test to assess HER2 mutation status in tumor tissue samples from patients with non-small cell lung cancer treated with Trastuzumab Deruxtecan in the DESTINY-Lung01 and DESTINY-Lung02 studies. Qi Z, Ha T, Feng W, Kamoub M, Pereira K, Shiga R, Smith EF, Coto Y, Johannes De Langen A, Coto K, Velasco Roth AM, Khambata-Ford S. Arch Pathol Lab Med. 2025;149:542-549.

Background: Accurate identification of HER2 mutations is essential for selecting patients who may benefit from Tastuzumab deruxteca (T-DXd). The Oncomine Dx Target (ODxT) Test is a next-generation sequencing (NGS) assay, which was evaluated in this paper as a companion diagnostic (CDx) tool for the detection of HER2 mutation in NSCLC.

Methods:

Study Design: Analytical and clinical validation of the ODxT Test using retrospective tumor samples from DESTINY-Lung01 and DESTINY-Lung02 (both phase 2 trials), and commercially procured NSCLC samples.

Analytical Validation: Compared ODxT results to those from the TruSight Tumor 170 (TST170) assay, an orthogonal NGS assay.

Clinical Validation: Compared ODxT Test results to clinical trial assays (CTAs) used for enrollment in the DESTINY trials.

Tumor Samples: FFPE tissue blocks or slides, requiring ≥10% tumor content and 10 ng DNA input.

HER2 Mutation Detection: 41 activating HER2 mutations were targeted; differences in mutation panels existed between Lung01 and Lung02.

Concordance Criteria: Prespecified thresholds of ≥90% for analytical positive/negative percent agreement (PPA/NPA) and FDA benchmarks for clinical concordance.

Results:

| Category | Study/Comparison | Metric | Result | Notes |
|---|---|---|---|---|
| **Analytical Accuracy** | Compared to TST170 assay | PPA | 100% | Met prespecified threshold (>90%) |
| | | NPA | 99.1% | |
| **Clinical Accuracy** | DESTINY-Lung01 | PPA | 98.0% | Met FDA requirements for clinical validation |
| | | NPA | 100% | |
| | DESTINY-Lung02 | PPA | 96.7% | |
| | | NPA | 100% | |
| **Clinical Utility** | DESTINY-Lung01 | ORR | 58.3% (ODxT) vs 54.9% (CTA) | Comparable efficacy between ODxT and CTA |
| | | DoR | 12.0 mo (ODxT) vs 9.3 mo (CTA) | |
| | DESTINY-Lung02 | ORR | 53.6% (ODxT) vs 53.8% (CTA) | |
| | | DoR | Data immature | |

Discussion: The ODxT test demonstrated high analytical and clinical accuracy in detecting HER2 mutations in NSCLC. It demonstrated high concordance with existing reference and clinical trial assays and comparable clinical outcomes in patients treated with T-DXd. It reliably identifies patients who are likely to benefit from the T-DXd treatment, which supports its use as a companion diagnostic test in clinical settings.

Comment: Interesting test that could facilitate faster, decentralized biomarker testing. But limited by only including SNVs and exon 20 insertions. Her2 ampliciation/overexpression are not validated, and novel Her2 mutations would be missed (as seen with 2 samples in this study).

2. Ex vivo fluorescence confocal microscopy for intraoperative evaluations of staple lines and surgical margins in specimens of the lung: a proof-of-concept study. Hildebrandt F, Kamm M, Titze B, Höink A, Vorwerk H, Sievert KD, Groetzner J, Titze U. Mod Pathol. 2025;38:100720.

Background: Evaluating staple line margins is highly problematic because metal clips interfere with sectioning and are not amenable to FS. Alternatives like cytology or modified staplers have limited applicability.
Ex vivo fluorescence confocal microscopy (FCM) offers a non-destructive, dye-based imaging method that generates high-resolution digital "pseudo-histologic" sections from unfixed tissue—already in use in dermatopathology and urology. This study explores its feasibility for intraoperative assessment of staple lines.
Methods:

- Study Population: 52 lung specimens from 51 patients (23 lobectomies, 5 segment resections, 24 wedge excisions).
- Specimens Examined:
  - 71 staple line margins, 8 anatomical (non-stapled) margins
- Technique:
  - FCM was performed intraoperatively using the VivaScope 2500-G4.
  - Specimens were briefly stained with acridine orange and scanned in both fluorescence and reflection mode.
  - FCM images were compared to FFPE sections of the same material.
  - Margin status was evaluated by two pathologists (one intraoperative, one blinded post hoc).
- Endpoints:
    - Visualization of stapled margins.
    - Diagnostic accuracy of FCM in detecting tumor at margins.
- Statistical Analysis:
  - Margin status classified as benign, tumor present, or suspicious.
  - Agreement assessed via Cohen's kappa.

Results:

- Staple Lines:
  - FCM could image staple line tissue without removing clips.
  - Tumor at margins detectable based on nuclear atypia, architecture, and fluorescence signal.
  - Of 4 tumor-involved staple lines), 3 were correctly identified by both raters.
  - Kappa: 0.70 (U.T.), 0.65 (B.T.) — *substantial agreement*.
- Comparison with FS:
  - FS of re-inked artificial margins showed *moderate agreement* with final histology (kappa = 0.52).
  - FCM had higher specificity (100% vs. 94%) and better PPV (100% vs. 43%) than FS.
  - False positives were fewer with FCM than with FS.
- Turnaround Time:
  - Average FCM scan time: 7 minutes.
  - Often completed before FS results were communicated.

Discussion: FCM enabled intraoperative visualization of true staple line margins without removing metal clips. It was diagnostically accurate, reduced false positives compared to FS, and had turnaround times compatible with intraoperative workflows. This method offers a promising supplemental or alternative strategy for assessing margins in lung resections, especially when FS is limited by staple interference.

Comment: Interesting concept. No mention of training on recognition of tumor. Future directions should include: Validation in larger cohorts, Evaluation across diverse tumor types (e.g., STAS-positive adenocarcinomas), Development of FCM-compatible inks.

3. Long COVID in immunocompromised and immunocompetent patients: a clinical, morphologic, and virologic portrait. Ramalhosa F, Lunardi F, Bernardinello N, Cori S, Pezzuto F, Tauro V, Del Veccio C, Giraudo C, Balestro E, Calabrese F. Arch Pathol Lab Med. 2025;149:535-541.

   Background: COVID-19 primarily affects the lungs that can lead to chronic/post-COVID syndrome. There is limited data on the lungs of patients with long COVID.
   Methods: A retrospective observational study to evaluate morphologic and viral features in Tbbx of immunocompetent and immunocompromised COVID patients. Several histologic changes analyzed with computer-assisted morphometry. Tissue SARS-CoV-2 including subgenomic transcripts were investigated.
   Results: Inclusion criteria: SARS-CoV-2 pneumonia at least 30 days before with persistent lung involvement on HRCT (> 10% involvement) and respiratory or systemic symptoms after at least 12 wks from infection. Exclusion criteria: severely compromised lung function or resting hypoxemia. Control group of 28 patients were selected from pre-COVID cohorts. HRCT assessed by expert thoracic radiologists.

   All slides reviewed digitally (QuPath computer assisted morphometric analysis) of fibrosis and inflammation were also performed.

   18/457 patients with post-COVID underwent TBBx, because the extent of lung damage was greater than 10% radiographically and there were no contraindications indications for biopsy. 50% were immunocompetent and 50% immunocompromised (all lung transplant recipients).

   In all long-COVID patients, OP was the dominant finding (78%).

   Patients also had evidence of vascular damage characterized by “post-hyalinization and remodeling”.

   14/18 controls shared vascular alterations consisting of vessel hyalinization and hemosiderosis.

   Quantification showed long-COVID biopsies showed significantly lower inflammation than OP controls (18.8% versus 30.8%, $P$ <.001) despite similar fibrotic extensions (33.9% versus 36.3%).

   The degree of inflammation was similar between immunocompromised and immunocompetent hosts. However, the “extension of fibrosis” was significantly higher in long-COVID immunocompetent than immunocompromised patients (44.9% versus 19.6%, *P=.05).*

   Tissue SARS-CoV-2 transcripts were identified in 3 long COVID patients (2 immunocompromised and 1 immunocompetent).

   Discussion: The dominant finding in these patients was that of organizing pneumonia. Vascular changes were also present although the control patients had similar findings. The authors suggest their vascular findings tended toward significant and that perhaps low numbers account for the lack of statistical significance. They also comment that in their group of long-COVID patients the amount of inflammation associated with OP was less than controls (in contrast to another recent study which showed the opposite).

   Comment: I found the paper challenging because of unusual grammatical usage. It took me a while to figure out that fibrosis extension meant amount of fibrosis (I think). It’s also poorly illustrated with only very low power images. Rather, there is a whole page for Figure 1 which I think is unnecessary. I would rather have seen more high-power pathology images to help the authors make their point e.g vascular pathology not shown. Exclusion criteria also significant. I don’t think there is very much new here.

4. IASLC grading system predicts distant metastases for resected lung adenocarcinoma. Wang Y, Smith MR, Dixon CB, D'Agostino R, Liu Y, Ruiz J, Chan MD, Su J, Mileham KF, Lycan T, Green ME, Hassan OA, Jiang Y, Khan Niazi MK, Li W, Xing F. J Clin Pathol. 2025;8:409-415.

   Background: This study was designed to assess the potential of IASLC grading system for lung adenocarcinoma (LUAD) in predicting the occurrence of brain and bone metastases in patients.

   Methods: Retrospective review of clinical data and pathology reports of 174 patients w/ early stage LUAD, resected 2008- 2015. Minimum follow-up 5 years. Predominant pattern-based grading was obtained from original pathology reports and cases were reassessed by 3 pathologists according to IASLC system. Patients excluded: previous lung cancer, other cancers or disease that might affect 5-year survival, mucinous adenocarcinoma, lost to follow-up. Cases were reviewed by two pathologists and shared with a third when they were discrepancies. Statistical analysis performed with generation of ROC curves.

   Results: During the 5-year follow-up 28 patients (16%) developed distant mets resulting in an overall median survival of 38.3 months compared to 60 months for patients without distant mets. Stages as follows: Stage I: 122 (70%); Stage II: 37 (21.3%); and Stage III: 15 (8.6%).

   According to IASLC grading: Grade 1: 23 patients (13.4%); Grade 2: 58 (34.6%); and Grade 3: 93 (52%). LVI observed in 29 patients (16.8%).

   Both the original prodminant grading system and the IASLC grading system showed a correlation between higher tumor grade and reduced overall survival. However, there was a significant difference in OS between patients with grade 2 and grade 3 tumors only in the IASLC grading group.

   Under the IASLC system, higher tumor grade correlated with increased incidence of distant mets in the presence of LVI. These metastases free survival of 28 patients based on IASLC grading and stage shows that it could segregate grade 2 and grade 3 patients while tumor stage failed to do so. ROC analysis also showed that IASLC grading showed better predictive value for distant mets compared with tumor stage.

   Additional analysis showed IASLC grading system could segregate patients brain metastasis free survival between grade 3 and grade 1 or 2 tumors.

   However, a significant difference in met free survival was only found in patients with stage 1 and 3 tumors. ROC analysis also demonstrated superior predictive power of IASLC grading compared to tumor stage.

   Similar results obtained for patients with bone mets where the IASLC grading system but not stage effectively distinguished grade 2 and grade 3 patients based on bone metastasis free survival analysis.

   Further analysis showed lepidic pattern was observed in tumors from met free patients while complex glandular patterns were highly prevalent in sections derived from patients with distant metastases.

   Discussion: Interesting that the IASLC grading system out performed tumor stage in predicting occurrence of distant mets. Highlights that there is no integrative predictive model incorporating grade with other pathologic features including nuclear and mitotic grade, STAS and LVI.

   Comment: Overall, a reasonable study supporting utility of the IASLC grading system. It's disappointing when studies delete mucinous carcinomas from the analysis in some way.

Neoplastic

1. Navigational bronchoscopy or transthoracic needle biopsy for lung nodules. Lentz RJ, Frederick-Dyer K, Planz VB, Koyama T, Aboudara MC, Avasarala SK, Casey JD, Cheng GZ, D'Haese PF, Duke JD, Grogan EL, Hoopman TC, Johnson J, Katsis JM, Kuman JS, Low SW, Mahmood K. Rickman OB, Roller L, Salmon C, Shojaee S, Swanner B, Wahidi MM, Walston C, Silvestri GA, Yarmua L, Rahman NM, Maldonado F, for the Interventional Pulmonary Outcomes Group. N Engl J. Med. 2025;391:2100-12.

This multicenter, randomized, noninferiority trial (VERITAS) compared the diagnostic accuracy and complication rates of navigational bronchoscopy (NB) versus CT-guided transthoracic needle biopsy (TTNB) for peripheral pulmonary nodules measuring 10–30 mm in patients with ≥10% pretest probability of malignancy.

Key elements include:

- Diagnostic accuracy was 79.0% for NB and 73.6% for TTNB, with a noninferiority margin of 10 percentage points achieved (P = 0.003).
- False negatives occurred only in the TTNB group (3.6%).
- Pneumothorax rates were significantly lower in the NB group (3.3%) compared to TTNB (28.3%), with fewer severe cases requiring intervention (0.8% vs 11.5%).
- Nodules were mostly solid (82.5%) and located in the outer third of the lung (87.6%), with a median diameter of 15 mm.
- NB utilized advanced imaging (digital tomosynthesis) and had higher use of rapid on-site cytologic evaluation (95.8% vs 7.2%).

Histologically, both modalities identified malignancy and specific benign lesions (e.g., granulomatous inflammation, organizing pneumonia), but NB showed a trend toward fewer nondiagnostic results and a broader range of benign diagnoses.

Summary: NB is noninferior to transthoracic needle biopsy for peripheral lung nodules and carries a significantly lower risk of complications, especially pneumothorax. It should be considered a first-line option when technically feasible, particularly in smaller nodules or when minimizing risk is critical.

Non-Neoplastic

1. Nerandomilast in patients with progressive pulmonary fibrosis. Maher TM, Assassi S, Azuma A, Cottin V, Hoffmann-Vold AM, Kreuter M, Oldham JM, Richeldi L, Valenzuela C. Wijsenbeek MS, Clerisme-Beaty E, Coeck C, Gu H, Ritter I, Schlosser A, Stowasser S, Voss F, Weimann G, Zoz DF, Martinez Fj, for the FIBRONEER-ILD Trial Investigators. N Engl J Med. 2025;392:2203-14.

This phase 3 randomized controlled trial (FIBRONEER-ILD) evaluated the efficacy and safety of nerandomilast, a selective oral PDE4B inhibitor, in patients with progressive pulmonary fibrosis (PPF). The study included 1176 patients with non-IPF fibrotic ILD who met specific criteria for disease progression.

Patients were randomized 1:1:1 to receive nerandomilast 18 mg BID, 9 mg BID, or placebo for 52 weeks. Background therapy with nintedanib was allowed. The primary endpoint was the absolute change in FVC (mL) at week 52. The trial population included a mix of fibrotic ILD diagnoses, such as autoimmune ILD, hypersensitivity pneumonitis, and unclassifiable IIP. About 70% of patients had a UIP or UIP-like pattern on HRCT.

- The decline in FVC was:
  - −98.6 mL with 18 mg nerandomilast
  - −84.6 mL with 9 mg nerandomilast
  - −165.8 mL with placebo
- Both doses significantly slowed FVC decline compared to placebo:
  - 18 mg: +67.2 mL difference ($p<0.001$)
  - 9 mg: +81.1 mL difference ($p<0.001$)

Mortality and other key secondary outcomes also trended in favor of nerandomilast:

- Death: 6.1% (18 mg), 8.4% (9 mg), 12.8% (placebo)
- Hazard ratio for death: 0.48 (18 mg) and 0.60 (9 mg) vs. placebo

Adverse events were similar across groups, with diarrhea being the most common (up to 36.6% in the 18 mg group). Discontinuation due to side effects was infrequent.

Summary: Nerandomilast, at both 18 mg and 9 mg BID doses, significantly slowed the decline in lung function over one year in patients with progressive pulmonary fibrosis, regardless of background nintedanib therapy. The drug was generally well tolerated. This supports nerandomilast as a potential new therapeutic option for non-IPF fibrosing ILDs with a progressive phenotype.

2. Richeldi L, Azuma A, Cottin V, et al. *Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis.* N Engl J Med. 2025;392(22):2193–2202. doi:10.1056/NEJMoa2414108.

This phase 3, double-blind, placebo-controlled trial (FIBRONEER-IPF) evaluated nerandomilast (BI 1015550), a selective phosphodiesterase 4B (PDE4B) inhibitor, in 1177 patients with idiopathic pulmonary fibrosis (IPF) over 52 weeks. Participants were randomized to receive nerandomilast 18 mg BID, 9 mg BID, or placebo, with or without background antifibrotic therapy (nintedanib or pirfenidone).

- Primary endpoint: Change in forced vital capacity (FVC) at 52 weeks.
- Results:
  - FVC decline was −114.7 mL (18 mg), −138.6 mL (9 mg), and −183.5 mL (placebo).
  - Statistically significant preservation of lung function with both nerandomilast doses vs placebo.
  - Subgroup analyses showed the benefit was generally consistent, although efficacy was reduced in pirfenidone users (due to ~50% lower plasma levels of nerandomilast).
- Adverse events:
  - Diarrhea was the most common, especially with background nintedanib.
  - Serious adverse events were similar across groups.
  - No increased risk of depression, suicidality, or liver injury.

Histologically, all participants had confirmed UIP or probable UIP patterns on HRCT; some had biopsy-proven IPF if HRCT was indeterminate.

Summary: Nerandomilast, particularly at 18 mg twice daily, significantly slows FVC decline in IPF, with a manageable safety profile. It may be useful as monotherapy or adjunct therapy, though its efficacy may be diminished when used with pirfenidone due to pharmacokinetic interaction.

3. Spontaneous resolution in autoimmune pulmonary alveolar proteinosis: a case series. Sahoo S, Saxena P, Ravi AK, Tiwari S, Muthu V, Avala RC, Gella V, Gandra RR, Choudhary R. Chest. 2025;167(6):e177-e181.

This case series describes three patients with autoimmune pulmonary alveolar proteinosis (APAP) who exhibited spontaneous clinical and radiologic resolution of their disease despite presenting with moderate-to-severe hypoxemia.

All patients had documented occupational exposure to noxious inhalational agents such as gasoline, kerosene, and industrial fumes (including mercury and isocyanates), and all showed elevated anti-GM-CSF antibody levels, confirming the autoimmune subtype. Despite either refusing or discontinuing standard treatments such as whole lung lavage (WLL) or GM-CSF therapy, all three cases improved following removal from further exposure.

Histologic and ultrastructural findings consistent with PAP included periodic-acid Schiff (PAS)-positive intra-alveolar material, foamy macrophages, and lamellated surfactant bodies on electron microscopy. Radiologic features showed typical crazy-paving patterns that improved on follow-up imaging.

The authors suggest a "double-hit" mechanism, where environmental exposures may exacerbate or unmask the underlying autoimmune disease, and cessation of exposure may allow for recovery in some cases.

Even in patients with hypoxemic APAP, spontaneous resolution may occur, particularly when noxious occupational exposures are discontinued. These findings challenge the assumption that severe disease always requires invasive therapy and highlight a potential environmental modifier in the pathogenesis of APAP.

4. Revisit of histopathology in rheumatoid lung nodules. Klaisuban W, Su C, Koslow M, Ryu JH, Tazelaar HD, Jenkins SM, Yi ES. Am J Surg Pathol. 2025;49:588-593.

This study presents a comprehensive histopathologic re-evaluation of pulmonary rheumatoid nodules (RN), comparing them with necrotizing infectious granulomas (IG) and granulomatosis with polyangiitis (GPA). A total of 28 surgically resected RNs were assessed alongside 33 IGs (histoplasmosis, mycobacterial infection, coccidioidomycosis) and 10 GPAs.

While many histologic features overlapped between RN, IG, and GPA—including necrosis type, presence of palisading histiocytes, and cavitation—the authors identified key differences primarily in the adjacent lung parenchyma:

- RN consistently lacked airspace granulomas and non-necrotizing granulomas, which were common in IG.
- Necrotizing vasculitis was absent in RN but present in nearly all GPA cases.
- RN showed a strong association with subpleural location, pleural fibrosis, chronic inflammation, cellular bronchiolitis, and basophilic necrosis.

Statistically significant features helpful in distinguishing RN from IG included presence of basophilic necrosis and absence of non-necrotizing granulomas. From GPA, RN was best distinguished by the absence of necrotizing vasculitis.

These findings support using adjacent lung features as a diagnostic adjunct in differentiating RN from its mimics, particularly in cases lacking definitive clinical or serologic context.

Summary: When evaluating necrotizing granulomas in the lung, the absence of airspace/non-necrotizing granulomas and necrotizing vasculitis in the background lung favors a diagnosis of rheumatoid nodule over infectious granulomas or GPA. Recognition of these histologic patterns can guide accurate diagnosis, especially when clinical data are limited.

Case Reports, Editorials, Reviews

1. A 47-year-old woman with recurrent fever and productive cough. Wang L, Sun X, Li Y, Peng M, Li X, Gao L, Feng R, Zhou Y, Shi J. Chest. 2025;167(6):e183-e188.

   Case of aspiration pneumonia.

This case report describes a 47-year-old woman with a 20-year history of recurrent postprandial cough and expectoration of food particles, later complicated by fever and right-sided pleuritic chest pain. Initial evaluations—including chest CT and bronchoscopy—led to a misdiagnosis of hypersensitivity pneumonitis, supported by transbronchial cryobiopsy showing Masson bodies and foreign body granulomas.

2. Meijer-Jorna, L.B., & Thunnissen, E. In Compressed Lung Tissue Microscopic Sections of Adenocarcinoma In Situ May Mimic Papillary Adenocarcinoma. Arch Pathol Lab Med. 2025;149(6):495. doi:10.5858/arpa.2024-0488-LE

In compressed lung tissue microscopic sections of adenocarcinoma in situ may mimic papillary adenocarcinoma. Meijer-Jorna LB, Thunnissen E. Arch Pathol Lab Med. 2025;149:495-496. This letter to the editor revisits and expands upon a 2013 publication that described how adenocarcinoma in situ (AIS) in compressed lung tissue can mimic papillary adenocarcinoma, potentially leading to diagnostic confusion. Recent studies have clarified that iatrogenic collapse of alveolar air spaces during specimen processing results in infolding of alveolar walls, generating a pseudopapillary or pseudoacinar morphology that may not reflect true invasion.

Two key updates are emphasized:

1. Biopsy vs. Resection Specimens: Biopsy samples are less prone to collapse, and the AIS morphology may be more readily identified in these. Recognizing this discrepancy can help avoid overcalling invasion in resection specimens that appear more complex due to artifact.
2. Gross Examination Limitations: AIS has a soft consistency similar to surrounding parenchyma, making it difficult to detect during gross inspection. A past case illustrates how a tumor was missed in initial slicing and only found during a second grossing pass.

An accompanying clinical follow-up supports the original diagnosis: a stable 5-mm lesion over 14 years aligns with the behavior of AIS rather than invasive carcinoma.

Summary:

- Be cautious when diagnosing invasion in lung adenocarcinoma, especially when observing papillary-like features in compressed resection specimens.
- Differences between biopsy and resection morphology, along with gross handling challenges, require heightened awareness to avoid overdiagnosis.
- This supports the call for potential modification to classification systems that account for iatrogenic changes in morphology.

3. Occlusive primary endobronchial amyloid tumour; a rare case. Curran JM, Steinfort D, Liu B. Thorax. 2025;80:400-401.

This report describes a rare case of a 69-year-old woman, a never-smoker with a past history of tuberculosis (treated in 1996), who presented with a 4-month history of productive cough and exertional dyspnea following a mild COVID-19 infection.

Initial imaging showed bulky left hilar and mediastinal lymphadenopathy with heterogeneous calcification. PET-CT revealed intense FDG uptake, raising concern for malignancy. Follow-up imaging demonstrated collapse of the left upper lobe, and bronchoscopy revealed a large obstructing endobronchial mass.

Histologic evaluation of the bronchial biopsy revealed amorphous eosinophilic material, which stained positively with Congo red and exhibited apple-green birefringence under polarized light—classic for amyloid. The diagnosis was tracheobronchial amyloidosis (TBA) manifesting as an endobronchial tumour, an exceptionally rare presentation.

Tracheobronchial amyloidosis typically presents with multifocal submucosal plaques; however, this case is unique in presenting as a solitary, occlusive endobronchial mass—not previously reported in the literature as causing complete bronchial occlusion.

4. Case 18-2025: A 63-year-old woman with dyspnea on exertion. Wood MJ, Maraboto Gonzalez CA, Goiffon RJ, Jacobsen ED, Hutchison BM. N Engl J Med. 2025;392:2459-70.

Case of Erdheim Chester Disease

Clinical Presentation: 63-year-old woman with dyspnea, fatigue, dry cough, abdominal distention, polydipsia, and polyuria.

- Medical History: Rheumatoid arthritis, diabetes, hypertension, prior meningioma.
- Imaging:
    - Chest CT: Pericardial thickening, pleural effusions, infiltrative mediastinal fat changes.
    - Abdominal MRI: Retroperitoneal soft tissue encasing kidneys and aorta; “hairy kidney” sign.
    - PET-CT: FDG uptake in mediastinum, pericardium, retroperitoneum, and bones.
    - Long bone CT: Bilateral sclerosis of femora/tibiae.
- Histology: Retroperitoneal biopsy showed foamy histiocytes, CD68+, CD163+, BRAF V600E+.
- Labs: Elevated ESR and CRP; normal IgG4 levels; confirmed central diabetes insipidus.

- Diagnosis: Erdheim–Chester disease, based on clinical, radiologic, histologic, and molecular findings.
- The patient was not a candidate for vemurafenib due to QTc prolongation.
- Treated with cobimetinib (MEK inhibitor).
- Response: Within a month, improved exercise tolerance; resolution of edema, polydipsia, and polyuria. PET imaging after 3 months showed regression of disease. Two years later, the patient remained in remission with minimal FDG activity.

5. Biopsy of peripheral lung nodules: inside out or outside in? Gould MK. N Engl J Med. 2025;391:2162-2163.

This editorial discusses evolving strategies for diagnosing peripheral pulmonary nodules, comparing the traditional "outside-in" approach of CT-guided transthoracic needle biopsy (TTNB) with the "inside-out" approach of advanced bronchoscopic techniques such as electromagnetic navigational bronchoscopy (ENB).

Newer bronchoscopic tools — including radial endobronchial ultrasound, digital tomosynthesis, and electromagnetic navigation — have extended the reach of bronchoscopy into the peripheral lung, offering a lower complication profile but previously limited diagnostic yield (~70%).

The editorial highlights a key study by Lentz et al. (2025), a multicenter randomized noninferiority trial comparing ENB with TTNB in patients with 10–30 mm peripheral nodules and intermediate/high cancer

probability. ENB showed noninferior diagnostic accuracy (79.0%) compared to TTNB (73.6%) and significantly fewer complications (notably pneumothorax requiring intervention).

Dr. Gould emphasizes the rigor of the Lentz trial, particularly its use of a well-defined measure of diagnostic accuracy confirmed by 12-month follow-up, addressing recent controversies over how "diagnostic yield" should be measured. However, he notes that operator expertise and institutional capabilities will significantly affect generalizability.

Advanced bronchoscopic approaches using real-time navigation and imaging can achieve diagnostic accuracy comparable to TTNB for peripheral lung nodules — with fewer complications. However, successful implementation depends heavily on local expertise and technology availability.

6. Case 17-2025: A 61-year-old man with respiratory failure and shock after kidney transplantation. Kotton CN, Cochran RL, Sanders AM, Safa K, Roth MT. N Engl J Med. 2025;392-2368-2378.

   Case of *Stronglyoides* infection

A 61-year-old man developed respiratory failure and septic shock 10 weeks after a deceased-donor kidney transplant for hypertensive nephrosclerosis. He presented with fatigue, emesis, abdominal pain, ileus, and progressive hypoxemia. Initial labs revealed leukocytosis, eosinophilia, hyponatremia, elevated creatinine, and glucose of 639 mg/dL. Imaging showed pulmonary edema, diffuse ground-glass opacities, mediastinal/hilar lymphadenopathy, and bowel distention.

- Tracheal aspirate: Numerous eosinophils and larval forms (250–300 μm), morphologically consistent with *Strongyloides stercoralis* (rhabditiform larvae).
- Skin biopsy: Dermal larval forms (12.5 μm in width), consistent with third-stage filariform *Strongyloides*.
- No strongyloides identified in the kidney wedge biopsy, although sample limitations prevented exclusion.
- Second transplant recipient also had stool positive for *Strongyloides*.

- Pulmonary involvement in disseminated strongyloidiasis includes interstitial infiltrates, ground-glass opacities, and diffuse eosinophilic inflammation.
- Recognition of larvae in tracheal aspirates or lung tissue is key for diagnosis.
- Histologic clues such as eosinophilic infiltration with larvae in tissue are essential for pathologists.

7. Editorial: Progress through persistence: turning the page in pulmonary fibrosis clinical trials. Lee JS. N Engl J Med. 2025;392:2267-2269.

This editorial by reflects on the evolution of clinical trial progress in idiopathic pulmonary fibrosis (IPF) and other progressive fibrosing interstitial lung diseases (ILDs). After a decade of stagnant therapeutic advances following the approval of nintedanib and pirfenidone in 2014, the recent publication of two Phase 3 trials (FIBRONEER-IPF and FIBRONEER-ILD) signals new hope. Both trials evaluated nerandomilast (BI 1015550), a selective PDE4B inhibitor with antifibrotic and immunomodulatory effects.

In both trials, nerandomilast at 9 mg and 18 mg doses significantly slowed FVC decline over 52 weeks compared to placebo. However, secondary endpoints such as acute exacerbation, hospitalization, or death showed no statistically significant differences, and quality-of-life measures remained unaffected. Importantly, diarrhea was a common side effect, especially with concurrent nintedanib use.

The editorial underscores persistent challenges: ongoing lung function loss despite treatment, the absence of mortality benefit clarity, and the need to better address symptom control and quality of life. The author emphasizes the importance of continued innovation, earlier ILD diagnosis, and potential shifts toward combination or early intervention therapy models.

8. Histopathologic and genetic distinction of well-differentiated grade 3 neuroendocrine tumor versus poorly differentiated neuroendocrine carcinoma in high-grade neuroendocrine neoplasms. Sun BL, Din H, Sun X. Am J Clin Pathol. 2025;163(6):804-814.

This comprehensive review highlights the key histologic and genetic differences between well-differentiated grade 3 neuroendocrine tumors (G3-NETs) and poorly-differentiated neuroendocrine carcinomas (NECs)—two entities that share high proliferation indices (Ki-67 >20%, mitoses >20/2 mm²) but diverge sharply in morphology, prognosis, and treatment response.

Key histopathologic features that favor G3-NETs include organoid architecture, monotonous nuclei with "salt-and-pepper" chromatin, and strong/diffuse neuroendocrine marker expression (e.g., chromogranin, synaptophysin). NECs, on the other hand, exhibit poorly-differentiated cytology (small or large cell patterns), sheet-like growth, and often lack typical neuroendocrine morphology.

Immunohistochemistry can help distinguish between the two:

- G3-NETs often show retained Rb, wild-type p53, and loss of ATRX/DAXX.
- NECs frequently show mutant p53, Rb loss, and lack ATRX/DAXX alterations.

Genetically, G3-NETs tend to have low tumor mutational burden (TMB) and mutations in MEN1, ATRX, and DAXX, whereas NECs exhibit high TMB and alterations in TP53 and RB1, as well as distinct pathway activations (e.g., PKA, TRK, GLI).

Therapeutically, this distinction is critical:

- G3-NETs are treated like lower-grade NETs with alkylating agents and somatostatin analogues.
- NECs require platinum-based chemotherapy due to their aggressive course.

Despite similar proliferative indices, G3-NETs and NECs are biologically distinct. A combination of morphologic evaluation, immunohistochemistry (TP53, Rb, ATRX/DAXX), and genetic profiling is essential to distinguish these entities and guide proper therapy. This differentiation has direct and critical implications for patient prognosis and treatment planning.

9. Invasive angiolipoma of the mediastinum and lung. Shang Z, Luo Y, Kang X, Hong C, Si Y. Thorax. 2025;80:398-399

A 12-year-old boy presented with a 1-month history of cough and exertional dyspnea. Imaging revealed a large, invasive mass in the mediastinum extending into the left lung and bronchus, with airway obstruction and vascular space involvement.

Bronchoscopy demonstrated significant airway narrowing due to both intrinsic tumor and extrinsic compression, but biopsy was deferred due to bleeding risk. A thoracotomy was performed for tumor debulking and tissue diagnosis.

Histopathologic examination revealed a borderless mass composed of vascular, adipose, and fibrous tissue. There was no cytologic atypia or mitotic activity.
Immunohistochemistry (IHC):

- CD31, CD34: Vascular positive
- S100: Adipocyte positive
- Desmin, SMA: Positive
- Ki-67: ~3%, indicating low proliferative activity

Diagnosis: Invasive angiolipoma involving the mediastinum and lung.

The patient recovered well postoperatively, but further bronchial resection was declined by the parents. No adjuvant therapy (e.g., radiotherapy) was given, and the patient was lost to follow-up.

10. Interstitial lipoid pneumonia: a complication of intravenous administration of lipid emulsions in critically ill patients. De Cuba EMV, Vreuls W, Tan CG, Flieder DB, Thunnissen E. Virchows Archiv. 2025;486:1339-1343.

This case report presents a rare instance of interstitial lipoid pneumonia caused by the intravenous administration of lipid emulsions (ILE) in a critically ill patient. The subject, a 61-year-old male, developed ARDS following a complicated postoperative course for symptomatic cholelithiasis. Management included total parenteral nutrition (TPN), dialysis, and mechanical ventilation. After worsening respiratory failure and pneumothorax, a lobectomy was performed. Histological findings revealed intra-alveolar hemorrhage and CD163-positive interstitial macrophages with intracytoplasmic fat droplets, confirmed via Oil-Red-O stain. These findings were consistent with interstitial lipoid pneumonia.

This diagnosis was further contextualized with radiologic findings (ground-glass opacities), and the authors emphasized that lipid-induced lung injury may be underrecognized in ICU patients receiving ILE. The case also includes an in-depth discussion of the differential diagnosis of clear-cell rich infiltrates in the lung, including aspiration-related lipoid pneumonia, storage diseases (e.g., Niemann-Pick), and infections (e.g., Whipple disease).

11. Bronchial Salivary gland-type mucinous adenocarcinoma harboring a GNAS mutation: a novel lung cancer entity? A case report. Chen C, Wu H, Yin W, Shi X, Zhao Y. Virchows Archiv. 2025;486:1327-1331.

This case report describes a 65-year-old man with a small (1 cm) mass in the left main bronchus. Histologically, the tumor displayed papillary, micropapillary, and cribriform architecture with abundant extracellular mucin, moderate to marked cytologic atypia, and evidence of vascular invasion. Notably, the tumor showed strong NKX3.1 expression, a marker of mucinous acinar cells of bronchial (salivary-type) glands, and lacked TTF-1, napsin A, P63, and other markers typical of conventional pulmonary adenocarcinomas.

Molecular profiling via next-generation sequencing revealed a GNAS p.R201C mutation—a genetic hallmark of pancreatic intraductal papillary mucinous neoplasms (IPMNs)—but no mutations in other common genes like KRAS, BRAF, or EGFR. This profile is reminiscent of salivary gland-type IPMN, an emerging low-grade mucinous tumor in the head and neck.

Gross and microscopic examination confirmed the tumor's submucosal location, close association with hyperplastic bronchial glands, and invasion into cartilage. Given its unique location, immunophenotype,

morphology, and genetics, the authors propose this as a novel pulmonary neoplasm, which they term “bronchial salivary gland-type mucinous adenocarcinoma.”

Differential diagnosis included mucous gland adenoma, colloid carcinoma, and ETV6-NTRK3 fusion-associated low-grade mucinous adenocarcinoma; however, these were excluded based on morphology, immunoprofile, and molecular findings. Importantly, the tumor may represent a malignant counterpart to mucous gland adenoma (MGA).

ERJ-Not a lot of pathology but lots of reviews and basic science about pulmonary fibrosis.

1. Editorial: Screening relatives of familial pulmonary fibrosis patients: who, when, how and why? Borie R, Kropski JA. Eur Respir J. 2025;65:2500019.

2. Editorial: Small packages but big insights: extracellular vesicles as biomarkers in interstitial lung disease associated with systemic sclerosis. Burgy O, Lehmann M. Eur Respir J. 2025;65:2402529.

3. Climbing the hierarchy of evidence in interstitial lung disease transcriptomics. Coyne LP, Ghosh AJ. Eur Respir J. 2025;65:2402471.

4. Editorial: Mapping idiopathic pulmonary fibrosis: how cellular niches fuel pathogenic plasma cell accumulation. Helou DG, Riteau N. Eur Respir J. 2025;65:2500036.

5. Accelerated epigenetic ageing worsens survival and mediates environmental stressors in fibrotic interstitial lung disease. Goobie GC, Marinescu DC, Adegunsoye A, Bourbeau J, Carlsten C. Clifford RL, Doiron D, Duan Q, Gibson KF, Grant-Orser A, Hernandez Cordero AI, Johannson KA, Kass DJ, Kim SE, Leung JM, Li X, Tan W, Yang CX, Nouraie SM, Ryerson CJ, Hackett TL, Zhang Y. Eur Respir J. 2025;65:2401618.

6. Association of fibrotic-related extracellular vesicle microRNAs with lung involvement in systemic sclerosis. Guiot J, André B, Potjewijd J, Jacquerie P, Cremers S, Henket M, Idoufkir L, Remacle C, Tobal R, Giltay L, Moermans C, Gester F, Polese B, Hamaïdia M, Struman I, Louis E, Malaise M, de Seny D, van Paassen P, Louis R, Ribbens C, Njock MS. Eur Respir J. 2025;65:2400276.

7. Transcriptomics of interstitial lung disease: a systematic review and meta-analysis. He D, Guler SA, Shannon CP, Ryerson CJ, Tebbutt SJ. Eur Respir J. 2025;65:2401070

8. Inhibition of AXL ameliorates pulmonary fibrosis via attenuation of M2 macrophage polarization. Kim DH, Kim HC, Im K, B IJ, Jung Y, Choi J, Lee H, Kim DS, Lee CW, Jeong JY, Ban K, Kim SY, Ji W, Lee JC, Kim HY, Lee Y, Yang Y, Yun M, Choi CM, Rho JK. Eur Respir J. 2025;65:2400615.

9. Editorial: Yapping about macrophages in fibrotic lung disease. Lafyatis R, Valenzi E. Eur Respir J. 2025;65:2500075.

10. Editorial: Targeting the AXL pathway: a promising strategy for pulmonary fibrosis. Larson-Casey JL, Carter AB. Eur Respir J. 2025;65:2500114.

11. YAP/TAZ are crucial regulators of macrophage-mediated pulmonary inflammation and fibrosis after bleomycin-induced injury. Mia MM, Abdul Bhani SAB, Cibi DM, Bogireddi H, Nilanthi U, Selvan A, Wong WSF, Singh MK. Eur Respir J. 2025;65:2301544.

12. Editorial: Theratyping in cystic fibrosis: filling the knowledge gaps. Pranke I, Sermet-Gaudelus I. Eur Respir J. 2025;65:2500778.

13. Relationship between theratyping in nasal epithelial cells and clinical outcomes in people with cystic fibrosis. Ratjen F, Stanojevic S, Gunawardena T, Eckford PDW, Avolio J, Shaw M, Bartlett C, Ouyang H, Moraes TJ, Gonska T, Bear C. Eur Respir J. 2025;65:2401855.

14. Protein biomarkers of interstitial lung abnormalities in relatives of patients with pulmonary fibrosis. Rose JA, Steele MP, Kosak Lopez EJ, Axelsson GT, Galecio Chao AG, Waich A, Regan K, Gulati S, Maeda AH, Sultana S, Cutting C, Tukpah AMC, Synn AJ, Rice MB, Goldberg HJ, Lee JS, Lynch DA, Putman RK, Hatabu H, Raby BA Schwartz DA, Rosas IO, Hunninghake GM. Eur Respir J. 2025;65:2401349.

15. Editorial: Building translational bridges in idiopathic pulmonary fibrosis research: from epithelial dysfunction to dysregulated macrophage polarization and fibrogenesis. Tsiri P, Beltramo G, Kolb M, Crestani B. Eur Respir J. 2025;65:2500938.

16. Editorial: Rejuvenation as a future for pulmonary fibrosis. Tsiri P, Crestani B. Eur Respir J. 2025;65:2500640.

17. Distinct mural cells and fibroblasts promote pathogenic plasma cell accumulation in idiopathic pulmonary fibrosis. Yang Z, Cao G, Tan X, Orfanos S, Jude J, Barbet G, An SS, Jiang D, Panettieri Jr RA, Yang Q. Eur Respir J. 2025;65:2401114.