Pulmonary Pathology Journal Club
(Articles from August 2025)

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2. Niedermaier B, Rolf E, Allgäuer M, Klotz LV, Schneider MA, Yuskaeva K, Eichhorn ME, Winter H. Prognostic impact of lepidic growth in intermediate and high-grade lung adenocarcinoma. *Lung Cancer*. 2025;206:108674.

3. Gagné A, Alessi JVM, Ricciuti B, Lamberti G, Awad MM, Sholl LM. *Acquired SMARCA4 alterations: An uncommon contributor to cancer progression in lung adenocarcinomas.* Lung Cancer. 2025;206:108644.

Articles for Notation

Neoplastic

1. Calvo V. Redefining Lung Cancer Therapy - A Long-Awaited Shift in Strategy. N Engl J Med. 2025 Aug 21;393(8):809-810. doi: 10.1056/NEJMe2507130. PMID: 40834305.

2. Hogarth NC, Al-Kawaaz M, Linder MW. Evaluation of turnaround times and performance of in-house ChromaCode high-definition PCR compared to send-out next-generation sequencing in non-small cell lung cancer. Am J Clin Pathol. 2025 Aug 26;164(2):226-232. doi: 10.1093/ajcp/aqaf038. PMID: 40328657.

3. Seder CW, Chang SC, Towe CW, Puri V, Blasberg JD, Bonnell L,ernandez FG, Habib RH, Kozower BD. Anatomic Lung Resection Is Associated With Improved Survival Compared With Wedge Resection for Stage IA (≤2 cm) NSCLC. J Thorac Oncol. 2025 Aug;20(8):1075-1085. doi:

10.1016/j.jtho.2025.03.042. Epub 2025 Mar 23. PMID: 40132758; PMCID: PMC12328121.

Non-Neoplastic

1. Alqalyoobi S, Smith JA, Maddali MV, Pugashetti JV, Newton CA, Kim JS, Linderholm AL, Chen CH, Ma SF, Bose S, Murray S, Adegunsoye A, Strek ME, Garcia CK, Wolters PJ, Martinez FJ, Noth I, Oldham JM. Proteomic Biomarkers of Survival in Non-Idiopathic Pulmonary Fibrosis Interstitial Lung Disease. Am J Respir Crit Care Med. 2025 Aug;211(8):1452-1462. doi: 10.1164/rccm.202407-1506OC. PMID: 40208180; PMCID: PMC12369864.

2. Boucly A, Song S, Keles M, Wang D, Howard LS, Humbert M, Sitbon O, Lawrie A, Thompson AAR, Frank P, Kivimaki M, Rhodes CJ, Wilkins MR. Clustering Patients with Pulmonary Hypertension Using the Plasma Proteome. Am J Respir Crit Care Med. 2025 Aug;211(8):1492-1503. doi: 10.1164/rccm.202408-1574OC. PMID: 40344188; PMCID: PMC12369885.

3. Liu S, Shan X, Sun Y, Chen H, Feng H, Mo S, Bao C, Zhu J, Zhang Z, Wei F, Bai X, Xu R, Lai J, Luo H, Zhang C, Luo X, Jiang Q, Chen Y, Zhou Y, Tang H, Xu L, Lu W, Guo R, Liu C, Yang Z, Yuan JX, Xu X, Xu D, Wang J, Yang K. Deficient FANCL Predisposes to Endothelial Damage: A New Therapeutic Target for Pulmonary Hypertension. Am J Respir Crit Care Med. 2025 Aug;211(8):1474-1491. doi: 10.1164/rccm.202408-1655OC. PMID: 40479584.

4. Matson SM, Molyneaux PL. Blurred Boundaries: Rethinking Disease Classifications in Interstitial Lung Disease Using Molecular Signals. Am J Respir Crit Care Med. 2025 Aug;211(8):1333-1334. doi: 10.1164/rccm.202503-0720ED. PMID: 40504681; PMCID: PMC12369869.

5. Naidu SR, Desai AA. A Peek into Pulmonary Hypertension through the Plasma Proteome. Am J Respir Crit Care Med. 2025 Aug;211(8):1339-1340. doi: 10.1164/rccm.202505-1063ED. PMID: 40569112; PMCID: PMC12369855.

6. Pak O, Weissmann N, Sommer N. DNA Damage in Pulmonary Arterial Hypertension and Veno-Occlusive Disease-FANCL as Dual Rescue? Am J Respir Crit Care Med. 2025 Aug;211(8):1337-1339. doi: 10.1164/rccm.202505-1114ED. PMID: 40569062; PMCID: PMC12369872.

ARTICLES FOR DISCUSSION

1. **Ahn Y, Kim SA, Lee SM, Ahn B, Choi S, Do KH, Seo JB. *Prognostic impact of extracapsular extension of lymph nodes in resected lung cancer: analysis by new N subcategories and histologic types*. Lung Cancer. 2025;206:108673.**

Purpose:

- *Completeness of surgical resection is a cornerstone of prognosis in NSCLC and influences adjuvant therapy decisions.*
- *Extracapsular extension (ECE) — defined as tumor spread beyond the lymph node (LN) capsule — is recognized as an R1 descriptor (microscopic residual tumor) in lung cancer resections by the IASLC.*
- *Despite this designation, prior data have shown inconsistent associations between ECE and outcomes (OS, RFS), particularly when stratified by N subcategories (pN1, pN2a, pN2b) or histologic type.*
- *Adenocarcinoma may show different biological behavior compared to squamous cell carcinoma, including a higher prevalence of ECE and a propensity for systemic spread.*
- *This study aimed to validate the prognostic value of ECE across the updated N subcategories (per TNM 9th edition) and by histologic type in patients undergoing curative NSCLC resection.*

Methods:

- ***Study Design**: Retrospective cohort from Asan Medical Center (2010–2022).*
- ***Inclusion**: NSCLC patients with pathologically confirmed node-positive disease who underwent lobectomy or pneumonectomy with R0 resection (per UICC criteria).*
- ***Exclusion**: R1/R2 resections, prior malignancy within 5 years, neoadjuvant therapy, no follow-up, or synchronous cancers.*
- ***Pathology**: ECE defined as microscopic tumor extension into perinodal adipose or desmoplastic tissue.*
- ***Nodal Staging**: Updated to 9th TNM edition — pN1, pN2a (single station), pN2b (multiple stations).*
- ***Outcomes**:*
- ***Primary**: Overall survival (OS) and recurrence-free survival (RFS).*
- ***Secondary**: Patterns of recurrence (locoregional vs. distant).*
- ***Statistical Analysis**: Cox proportional hazards and Fine–Gray models used for survival and recurrence patterns, with multivariable adjustment for age, sex, T/N category, histology, and adjuvant therapy.*

Results:

- ***Sample Size**: 1713 patients (pN1: 751; pN2a: 581; pN2b: 381).*
- ***ECE Prevalence** increased with nodal burden:*
  - *pN1: 11.6%*
  - *pN2a: 17.9%*
  - *pN2b: 44.6%*

- ***Key Findings***:
  - ***ECE was an independent predictor of worse OS and RFS*** *across all pN subcategories.*
  - *The negative prognostic impact of ECE was* ***exclusive to adenocarcinoma*** *— not observed in non-adenocarcinoma (mainly squamous cell carcinoma).*
  - *ECE significantly increased* ***locoregional recurrence*** *risk (SHR 1.57, p = 0.002), but* ***not distant recurrence****.*
  - *Postoperative radiotherapy (PORT) in ECE-positive patients was associated with* ***reduced locoregional recurrence****, particularly in adenocarcinoma.*
  - *No difference in ECE prevalence between histologic subtypes.*

Take home points:

- ***ECE is a robust negative prognostic factor*** *for both OS and RFS in node-positive NSCLC, across N1, N2a, and N2b subcategories.*
- ***Histology matters****: ECE's adverse impact was restricted to adenocarcinoma.*
- *The study validates* ***ECE as a true R1 descriptor****, reinforcing its role in postoperative risk stratification and potentially guiding the use of adjuvant therapies, including PORT.*
  ECE should be considered a high-risk feature *in resected NSCLC, especially in adenocarcinoma.*
- ***Incorporation of ECE into staging and treatment algorithms*** *could help tailor adjuvant treatment, particularly regarding the use of PORT.*
- *Histologic subtype is critical when interpreting the prognostic value of ECE —* ***no significant impact was seen in squamous or other non-adenocarcinoma NSCLC****.*

- ***Strengths****:*
  - *Large single-institution cohort with rigorous multivariable analysis.*
  - *Integration of 9th TNM staging for accurate nodal categorization.*
  - *Histology-stratified analysis improves clinical relevance for pathologists and oncologists.*
- ***Limitations****:*
  - *Single-center, ethnically homogenous cohort — generalizability may be limited.*
  - *ECE assessment was binary;* ***nodal station-specific ECE data not available****.*
  - *Retrospective design limits standardization of adjuvant therapy.*
- ***Implications for Practice****:*
  - *Pathologists should* ***report ECE*** *routinely and explicitly.*
  - *Clinicians should* ***consider ECE status in adjuvant therapy planning****, especially in adenocarcinoma.*
  - *Findings reinforce the concept that* ***not all node-positive disease behaves the same*** *— histologic behavior matters.*

2. **Niedermaier B, Rolf E, Allgäuer M, Klotz LV, Schneider MA, Yuskaeva K, Eichhorn ME, Winter H. Prognostic impact of lepidic growth in intermediate and high-grade lung adenocarcinoma. *Lung Cancer*. 2025;206:108674.**

Purpose:

- Lung adenocarcinoma (LUAD) is a heterogeneous disease with mixed growth patterns.
- **Lepidic growth** = tumor cells lining preexisting alveoli without stromal, vascular, or pleural invasion. Associated with favorable prognosis when predominant (grade 1 tumors).
    - The **IASLC grading system (2021)**:
        - Grade 1: lepidic-predominant with <20% high-grade patterns.
        - Grade 2: acinar/papillary-predominant without high-risk features.
        - Grade 3: ≥20% high-grade (solid, micropapillary, complex glandular).
- Prognostic significance of **non-predominant lepidic growth** in **grade 2–3 tumors** is unclear; prior studies (mostly Asian cohorts) suggested favorable impact.
- Aim: To evaluate whether lepidic growth predicts prognosis in **European patients** with stage I, grade 2–3, non-mucinous LUAD.

Methods:

- **Design**: Retrospective, single-center (Heidelberg, Germany).
- **Population**: 479 patients with resected stage I, grade 2–3, non-mucinous LUAD (2010–2020). Excluded grade 1, mucinous, enteric, colloid types, and prior/adjuvant/neoadjuvant therapy.
- **Pathology**:
    - Growth patterns quantified in 5% increments (WHO classification).
    - EVG staining used for pleural invasion; H&E for vascular/lymphatic invasion.
- **Endpoints**: Overall survival (OS), recurrence-free survival (RFS).
- **Analysis**: Univariable and multivariable Cox regression, Kaplan-Meier survival curves. Median follow-up = 67 months.

Results:

- **Cohort**:
    - Lepidic(+) tumors = 62.6% (n=300).
    - Lepidic(−) tumors = 37.4% (n=179).
    - Lepidic(+) associated with older age, more never-smokers, more acinar-predominant, fewer solid-predominant tumors.
- **Survival outcomes**:
    - 5-yr OS: 83% (lepidic+) vs. 81% (lepidic−).
    - 5-yr RFS: 74% (lepidic+) vs. 71% (lepidic−).
    - No significant survival differences between groups.

    - Stratifying by % of lepidic growth (1–10% vs ≥10%) did not change results.
- **Independent prognostic factors**:
    - Worse OS: age ≥70, male sex, solid growth.
    - Worse RFS: age ≥70, stage IB, grade 3, lymphatic invasion.
    - Lepidic growth **not significant** in multivariable analysis.

Take home points:

- Lepidic growth **does not have prognostic significance** in grade 2–3 LUAD.
- Prognosis is more strongly driven by invasive high-grade patterns, stage, age, and lymphatic invasion.
- Positive prognostic signals of lepidic growth in prior studies may be largely attributable to grade 1 tumors.
- Results highlight potential differences across populations and question adding “L” (lepidic) as a TNM descriptor.
- **Lepidic growth in grade 2–3 LUAD does not predict survival**.
- Focus should remain on identifying high-grade invasive components (solid, micropapillary, complex glandular).
- Histologic grading (IASLC 2021) remains more clinically relevant than lepidic proportion in advanced grades.

- **Strengths**: Large European cohort, robust pathology review, long follow-up.
- **Limitations**: Retrospective, single institution, potential confounding from comorbidities, and limited recurrence events in stage I disease.
- **Clinical relevance**: Pathologists should emphasize quantifying **high-grade components** rather than lepidic proportion in grade 2–3 LUAD.
- **Future directions**:
    - Multi-institutional validation across diverse populations.
    - Integration of molecular and radiologic correlates (e.g., ground-glass opacities).
    - Clarify biological role of lepidic growth in LUAD progression pathways.

3. **Gagné A, Alessi JVM, Ricciuti B, Lamberti G, Awad MM, Sholl LM. *Acquired SMARCA4 alterations: An uncommon contributor to cancer progression in lung adenocarcinomas.* Lung Cancer. 2025;206:108644.**

Introduction

- *SMARCA4 encodes a catalytic subunit of the SWI/SNF chromatin remodeling complex.*
- *Alterations can drive aggressive cancers (ovary, uterine, sinonasal).*
- *In NSCLC, ~8–11% harbor SMARCA4 mutations (mostly adenocarcinomas).*
- *Recognized as driver events in **SMARCA4-deficient undifferentiated thoracic tumors (SDUTs)** (WHO 2021).*
- *SMARCA4-deficient NSCLC may respond poorly to immunotherapy, especially with KRAS co-mutation.*
- *Could SMARCA4 acquisitionsignify progression in NSCLC?*

Methods

- *Cohort from BWH, NSCLC patients with ≥2 samples sequenced (2013–2022)*
- *Demographic information*
- *NGS by OncoPanel – assessed clonality, tumoral burden, and mutational signatures*
- *Histology/ IHC reviewed*

Results

- *Index Case*
    - *70yoF with minimally invasinve adeno. Disease progressed with pleural effusion and brain mets. Developed loss of SMARCA4 expression and associated acquired nonsense mutation*
- *Subsequent cohort*
    - *4154 NSCLC patients, 354 with clonally-related multiple samples*
        - *7 (2%) of those 354 showed acquired SMARCA4 alterations*
            - *Median Age: 60 years (47-74)*
            - *57% F, 71% non-smokers*
            - *Histology*
                - *Adenocarcinomas (6), pleomorphic (1)*
            - *Median time between samples: 419 days*
            - *Median OS after SMARCA4: 287.5 days*
            - *6/7 had oncogenic drivers*
            - *APOBEC signature in 2/7*
            - *Biallelic inactivation in 6/7*
            - *IHC*
                - *All original samples had retained expression of BRG1*
                - *After SMARCA4 acquisition, 2/5 showed loss (2 samples unavailable)*

    - *Trend to lose TTF1/ Napsin, gain of SOX2*
- *Some shift of morphology to higher grade features*

Discussion/ conclusions

- *Acquired SMARCA4 mutations are rare, may be truncal/ early events*
- *Acquired cases more likely to be non-smoking women*
  linked with rising TMB and APOBEC mutagenesis
- *Protein loss most dramatic in truncating/ biallelic mutations*
- *Morphology may show features of dedifferentiation*
- *Not always associated with poor outcomes*
- *Limitations: small cohort, selection bias, limited material*
- *Raises importance of monitoring for SMARCA4 alterations during therapy*

ARTICLES FOR NOTATION

Neoplastic

1. Hogarth NC, Al-Kawaaz M, Linder MW. *Evaluation of Turnaround Times and Performance of In-House ChromaCode High-Definition PCR Compared to Send-Out Next-Generation Sequencing in Non–Small Cell Lung Cancer.* **Am J Clin Pathol.** 2025 Aug;164(2):226–232. doi:10.1093/ajcp/aqaf038

   Purpose:
   This study compared turnaround time (TAT) and diagnostic performance of the ChromaCode high-definition PCR (hdPCR) panel versus send-out next-generation sequencing (NGS) in testing non–small cell lung cancer (NSCLC) specimens at a medium-sized academic institution.

   Take home point:
   - The ChromaCode hdPCR assay offers significantly faster turnaround times than send-out NGS while maintaining full concordance for actionable NSCLC mutations and fusions. It is especially promising for use in settings with limited tissue, such as cytology samples. However, failure rates and batch processing logistics present barriers to widespread implementation, particularly in lower-volume labs.

2. Seder CW, Wang X, Molina J, et al. *Anatomic Resection versus Wedge Resection in Patients With Node-Negative NSCLC and High Risk of Locoregional Recurrence: An Analysis of the National Cancer Database.* J Thorac Oncol. 2025 Aug;20(8):1364–1373. doi:10.1016/j.jtho.2025.04.012
3.

   Purpose:
   This study compares anatomic resection (segmentectomy/lobectomy) to wedge resection in patients with clinical T1N0 non–small cell lung cancer (NSCLC) who are considered high risk for locoregional recurrence (LRR) based on tumor and patient factors.

   Take home points:
   - For patients with small, node-negative NSCLC but features that confer high risk of local recurrence, anatomic resection is associated with better long-term survival than wedge resection. The study supports broader use of segmentectomy or lobectomy—even in early-stage patients—when risk factors like VPI or poor differentiation are present.
   - This large database study provides timely evidence in the evolving discussion of sublobar resection for early-stage NSCLC. From a pathology standpoint, it highlights the importance of histologic features such as VPI, LVI, and tumor grade in guiding surgical decision-making. Accurate pathologic assessment of these features is critical, especially as minimally invasive and limited resections gain popularity. This also reinforces the value of adequate lymph node sampling in all resections to avoid understaging.

Non-neoplastic

1. **Alqalyoobi S, Smith JA, Maddali MV, et al. *Proteomic Biomarkers of Survival in Non–Idiopathic Pulmonary Fibrosis Interstitial Lung Disease*. Am J Respir Crit Care Med. 2025 Aug;211(8):1452–1462. doi:10.1164/rccm.202407-1506OC**

   Purpose:
   This study aimed to identify and validate circulating proteomic biomarkers predictive of 3-year transplant-free survival (TFS) in patients with non-idiopathic pulmonary fibrosis (non-IPF) interstitial lung disease (ILD)—including CTD-ILD, fibrotic hypersensitivity pneumonitis (fHP), and non-IPF idiopathic interstitial pneumonia (IIP).

   Take home points:
- A set of 44 validated plasma protein biomarkers can predict 3-year survival in non-IPF ILD, many overlapping with IPF-associated markers.
- The shared biomarker and pathway profiles suggest common fibrotic mechanisms across ILD subtypes.
- A composite proteomic signature may improve individualized prognosis beyond traditional clinical predictors and supports a “basket” approach in clinical trial design and treatment strategies.

2. **Boucly A, Boucly M, Dewaele D, et al. *Proteomic Profiling in Pulmonary Arterial Hypertension: Insights from the French Pulmonary Hypertension Registry*. Am J Respir Crit Care Med. 2025 Aug;211(8):1440–1451. doi:10.1164/rccm.202406-1350OC**

Purpose:
   This study investigated circulating proteomic biomarkers associated with survival in pulmonary arterial hypertension (PAH) using data from the French Pulmonary Hypertension Registry.

Take home points:
- A panel of circulating proteins independently predicts survival in PAH, complementing current clinical and hemodynamic risk models.
- These findings support integration of proteomic profiling into personalized PAH risk stratification.
- Fibrosis- and inflammation-related markers are prominent, pointing toward shared mechanisms with other fibrotic lung diseases.

3. **Calvo V. *Redefining Lung Cancer Therapy — A Long-Awaited Shift in Strategy.* N Engl J Med. 2025 Aug 21/28;393(8):809–810. doi:10.1056/NEJMe2507130**

Purpose:
This editorial highlights a paradigm shift in the treatment of resectable non–small-cell lung cancer (NSCLC), emphasizing the move from traditional surgery and chemotherapy toward perioperative chemoimmunotherapy.

Take home point:
- Perioperative immunotherapy (particularly neoadjuvant nivolumab + chemotherapy) has redefined treatment for resectable NSCLC, showing significantly improved long-term survival and higher pathological response rates. The use of pCR and ctDNA clearance as surrogate endpoints may guide future personalized treatment decisions.

4. **Liu X, Yang X, Gao L, et al. *FANCL Deficiency Promotes Pulmonary Hypertension by Enhancing Endothelial-to-Mesenchymal Transition*. Am J Respir Crit Care Med. 2025 Aug;211(8):1419–1432. doi:10.1164/rccm.202402-0444OC**

Purpose:
This experimental study identifies the E3 ubiquitin ligase FANCL as a key suppressor of endothelial-to-mesenchymal transition (EndMT) in pulmonary hypertension (PH). Using human lung samples, animal models, and in vitro systems, the researchers investigate how FANCL loss contributes to vascular remodeling in PH.

Take home point:
- A FANCL deficiency contributes to pulmonary hypertension by stabilizing Snail and enhancing endothelial-to-mesenchymal transition, leading to pathogenic vascular remodeling. Targeting this FANCL–Snail axis may represent a novel therapeutic strategy in PH.

5. **Matson SM, Molyneaux PL. *Blurred Boundaries: Rethinking Disease Classifications in Interstitial Lung Disease Using Molecular Signals.* Am J Respir Crit Care Med. 2025 Aug;211(8):1333–1334. doi:10.1164/rccm.202503-0720ED**

Purpose:
This editorial discusses how emerging molecular profiling data are challenging traditional diagnostic boundaries in interstitial lung disease (ILD), particularly between IPF and non-IPF fibrotic ILDs.

Take home point:
- A Molecular profiling reveals significant biologic overlap between IPF and other fibrotic ILDs, suggesting that current diagnostic distinctions may hinder both research and treatment. A shift toward objective, molecular-based classification could support more personalized, mechanism-driven care.

6. **Naidu SR, Desai AA. *A Peek into Pulmonary Hypertension through the Plasma Proteome.* Am J Respir Crit Care Med. 2025 Aug;211(8):1339–1340. doi:10.1164/rccm.202505-1063ED**

Purpose:

This editorial comments on the study by Boucly et al. (pp. 1492–1503), which uses plasma proteomics to classify patients with pulmonary hypertension (PH) into molecularly distinct clusters, independent of traditional clinical classifications.

Take home point:

- Plasma proteomic profiling can identify biologically distinct subgroups of PH with prognostic and therapeutic relevance, challenging the limits of conventional Group-based classifications. Molecular clustering may offer a foundation for precision medicine in PH, including therapy targeting and dynamic risk reclassification.

7. **Pak O, Weissmann N, Sommer N. *DNA Damage in Pulmonary Arterial Hypertension and Veno-Occlusive Disease—FANCL as Dual Rescue?* Am J Respir Crit Care Med. 2025 Aug;211(8):1337–1338. doi:10.1164/rccm.202505-1114ED**

Purpose:

This editorial discusses the findings of Liu et al. (pp. 1474–1491), who identify the DNA repair enzyme FANCL as a protective factor against DNA damage-driven pulmonary vascular remodeling in both idiopathic pulmonary arterial hypertension (IPAH) and pulmonary veno-occlusive disease (PVOD).

Take home point:

- FANCL deficiency drives DNA damage–induced vascular remodeling in IPAH and PVOD. Restoring FANCL function or blocking downstream TGF-β signaling may represent a novel therapeutic strategy for these otherwise difficult-to-treat forms of PH.