Pulmonary Pathology Journal Club – February 2026

Articles from January 2026 Journals

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Articles for Discussion

1. **Zhao M, et al. Recurrent PDGFRB Mutations in Pulmonary Microcystic Fibromyxoma: A Clinicopathologic and Molecular Analysis of 3 Cases. American Journal of Surgical Pathology. 2026;50(1):41-50.**

Background

Pulmonary microcystic fibromyxoma (PMF) is an exceptionally rare benign mesenchymal tumor of the lung, with fewer than 10 cases in literature

- Presents as a solitary, peripheral pulmonary nodule
- Histologically distinctive but diagnostically challenging
    - Well-circumscribed peripheral lesion
    - Prominent microcystic architecture
    - Bland stellate-to-spindled cells
    - Fibromyxoid stroma
    - No mitoses or necrosis
    - Entrapment of benign alveolar epithelium at periphery
- Lacks lineage-specific immunohistochemical markers
- Morphologic overlap with numerous primary and metastatic myxoid neoplasms

Aim: To define the molecular pathogenesis of PMF.

Methods

Case Selection: 3 cases (2014–2024) that fulfilled criteria

- Microcystic architecture
- Bland stellate/spindled cells
- Fibromyxoid stroma
- No alternative lineage differentiation

Broad IHC panel performed

- Epithelial: AE1/AE3, EMA, TTF1
- Myogenic: SMA, desmin
- Neural: S100, SOX10
- Vascular: CD31, ERG, CD34
- Others: STAT6, MUC4, ALK, HMB45, Melan-A, etc.
- Ki67
- PDGFRB (performed in 1 case)

Molecular Testing

- DNA-based targeted NGS: 425-gene panel to detect SNVs, indels, CNAs and perform TMB assessment
- RNA-based targeted NGS: 201 fusion transcripts, especially designed to detect BST fusions

Results

Clinical Findings

- 2 males, 1 female; Age range: 48–63 years
- Mostly incidental findings
- All solitary peripheral lung nodules (1.5–3.5 cm), completely resected
- No recurrence or metastasis (mean follow-up 81 months)

Histologic Findings

Classic PMF morphology:

- Well-circumscribed, unencapsulated
- Prominent microcystic spaces
    - Filled with mucin, proteinaceous fluid, or blood
    - Lined by attenuated flattened cells
- Bland stellate/spindled stromal cells
- Alternating hypocellular/hypercellular zones
- Delicate capillary network
- No necrosis
- Mitotic activity <1/10 HPF
- Ki67 <2%
- One case showed: Peripheral reticular microcystic pattern and central hemorrhage

Immunophenotype

- Null immunophenotype reinforced
- 1 case positive for PDGFRB IHC (1 case): Diffuse cytoplasmic positivity with focal membranous enhancement

Molecular Findings

All 3 cases harbored PDGFRB mutations

Case	Mutation	Location
1	P.W566_I569del	Exon 12 (juxtamembrane)
2	P.R565_I569del	Exon 12 (juxtamembrane)
3	P.N666K	Exon 14 (kinase domain)

- These alterations are known activating PDGFRB mutations

<u>Take Home Message:</u>

- PMF is a rare benign pulmonary mesenchymal tumor with
    - Defining recurrent activating PDGFRB mutations (exon 12 & 14)
    - Characteristic microcystic fibromyxoid morphology
    - Null immunophenotype, making it a diagnosis of exclusion
    - Behaves in benign fashion
- PMF shares PDGFRB mutations with other tumors (myofibroma, myopericytom, infantile myofibromatosis), BUT
    - Lacks perivascular architecture
    - Lacks SMA expression
    - Has unique pulmonary microcystic morphology
- Future aims
    - PDGFRB on tumors- Only performed in 1 case
    - See if this finding reproducible- Small cohort

2. **Naso JR, Sosa C, Schefter LE, et al. Gene expression signatures of shortened-telomere-associated fibrotic interstitial lung disease. Human Pathology. 2026;167:106006.**

Background

Subset of both sporadic and familial fibrotic interstitial lung disease (F-ILD) is associated with shortened telomeres, often related to pathogenic variants in telomere maintenance genes (e.g., *TERT, TERC*).

On lung histology. F-ILD in patients with shortened telomeres shows:

- Morphologic heterogeneity
- UIP and non-UIP patterns
- Frequent superimposed acute lung injury (ALI)
- Overlapping features with sporadic fibrosis

Mechanistic link between telomere shortening and fibrosis remains incompletely understood. Telomere dysfunction may promote:

- Alveolar epithelial cell senescence
- Aberrant wound repair
- Altered inflammatory signaling

Hypothesis: Immune and fibrosis-related gene expression pathways differ between shortened and non-shortened telomere F-ILD, potentially revealing mechanistic and therapeutic distinctions.

Methods

Study Cohort

- 39 lung explants (2015–2022), re-reviewed by 2 pathologists
  - 17 with shortened telomeres (<10th percentile in lymphocytes by flow-FISH)
  - 22 with normal telomere length
- Balanced representation of histologic diagnoses
  - UIP (51%)
  - NSIP
  - HP
  - CPFE
  - Unclassifiable fibrosis
  - Other
  - Note: ALI of any type was present in 59%.
- Telomere length assessed on peripheral blood lymphocytes
- Clinical genetic testing for telomere-related variants in a subset

Gene Expression Analysis

- Representative FFPE block selected and areas were avoided for microdissection
  - Pure end-stage fibrosis
  - Normal lung
  - Extensive acute lung injury
- NanoString nCounter Human Fibrosis v2 Panel (782 genes) and nCounter Master Kit
- Gene Expression Data obtained from Gene Expression Omnibus
- edgeR was used for differential gene expression analysis

Results

Cohort Characteristics

No significant differences between shortened vs non-shortened groups in:

- Age
- Sex
- Smoking history
- UIP vs non-UIP pattern
- Presence of superimposed ALI

Two shortened telomere cases had likely pathogenic *TERT* variants.

A. Pathway-Level Findings (GSEA)

Two major pathways were significantly enriched in shortened telomere lungs:

1. Cholesterol Metabolism (KEGG)

- Activated in shortened telomere group
- Upregulated genes included:
  - *APOA1*
  - *APOH*
  - *LIPC*
  - Multiple apolipoproteins

2. Regulation of TNF-Mediated Signaling

- GO terms significantly enriched
- Key genes:
  - *NR1H4* (FXR receptor)
  - *NCF4*
  - *RELN*
  - *MMP8*

B. Differentially Expressed Genes

36 genes significantly different (FDR < 0.05) between shortened vs non-shortened telomere cases

Notable genes (all increased in shortened group except *FGG*):

- **TNF-related:**
  - *NCF4*
  - *NR1H4*
- **Cholesterol metabolism:**
  - *APOA1*
  - *APOH*
  - *LIPC*
- Others:
  - *IL11*
  - *GLI1*
  - *ADIPOQ*
  - *LEP*
  - *CCR1*
  - *IL13*

C. Subgroup Effect

- Differential expression signal driven largely by **5 of 17 shortened telomere cases**

- One non-shortened telomere case clustered with this group
- Two of these cases had pathogenic *TERT* variants

These 6 distinct cases:

- More likely to have features of telomere biology disorder (premature greying, cirrhosis, family history)
- Not enriched for:
    - Dyslipidemia
    - Smoking
    - Antifibrotic therapy
    - Greater histologic fibrosis or inflammation

D. Spatial Transcriptomic Context

Using external GeoMx dataset:

- TNF signaling:
    - Higher in ILD vs normal lung
    - More prominent in inflammatory regions
    - Fibrotic regions showed relatively lower TNF activity
- Cholesterol metabolism:
    - Higher in fibrotic regions vs normal
    - APOA1 and NR1H4 enriched in fibrotic areas

Implication:

- Cholesterol metabolism signature likely arises from fibrotic compartments
- TNF activity may localize more to inflammatory regions

<u>Take Home Message:</u>

- Shortened telomere-associated F-ILD demonstrates molecular heterogeneity
- F-ILD patients with systemic (circulating lymphocytes) shortened telomeres are associated with altered cholesterol metabolism and TNF signaling signatures
- Key candidate mediators: *NCF4,* ***NR1H4*** **(FXR)**, ***APOA1****, APOH, LIPC*
- Potential therapeutic implications:
    - FXR agonists
    - Lipid-modifying therapies
    - TNF-pathway targeting strategies

3. **Pineda CM, O'Loughlin L, Benjamin HL, et al. Patterns of HER2 expression and genomic correlates in lung cancer, with a focus on preanalytical variables impacting immunohistochemical staining results. J Clin Pathol. 2026;79(1):24-30.**

Background

- Following disease-agnostic FDA approval of trastuzumab deruxtecan (T-DXd) for unresectable/metastatic HER2-positive (IHC 3+) solid tumors (DESTINY trials), HER2 IHC testing has become clinically relevant in lung cancer.
- However
    - HER2 testing is well standardized in breast and gastroesophageal cancer, but not in lung cancer.
    - Concordance between HER2 IHC and ERBB2 genomic alterations in lung tumors is poorly defined.
    - Preanalytical variables—especially fixation type (formalin vs alcohol-based cytology fixatives)—may significantly impact HER2 IHC interpretation.
- Study Aims
    - Analyze distribution of HER2 IHC staining in lung samples
    - See if IHC correlates with ERBB2 mutation/amplification
    - Correlate cytology and surgical biopsy HER2 IHC results

Methods

- Study Cohort
    - 166 thoracic tumor samples from patients potentially eligible for T-DXd
        - 119 surgical pathology specimens (biopsy or resection)
        - 47 cytology cell blocks (FNA, TBNA, effusions)- CytoLyt
    - HER2 IHC: Dako HercepTest. Scored per 2016 gastroesophageal HER2 guidelines
        - Only 3+ were considered positive
        - No reflex FISH was performed
    - Molecular Testing: FoundationOne CDx NGS for ERBB2 mutation/amplification
- Statistical analysis: Fisher's exact, ANOVA, Kruskal-Wallis

Results

- 13% of tumors were HER2 3+; most were HER2 0 (46%) followed by HER2 1+ (28%) and HER2 2+ (13%)
- HER2 3+ tumors were predominantly adenocarcinomas (90%)
- No significant differences in age, sex, smoking, race, TMB, or PD-L1 across HER2 groups
- Cytology specimens had significantly lower HER2 scores: Cytology HER2 0: 74% vs Surgical HER2 0: 35% ($p < 0.0001$)

    - Paired specimens (n=24, same site) showed 79% of cases showed decreased HER2 score on cytology as compared to surgical correlate
- ERBB2 Genomic Alterations (110 adenocarcinomas with NGS): 6% (7/110)
    - HER2 0: 9% had ERBB2 alteration
    - HER2 1+/2+: 0%
    - HER2 3+: 16%
- Among HER2 3+ cases:
    - Only 3/21 (14%) had ERBB2 genomic alterations
    - 81% had non-ERBB2 driver mutations, including:
        - KRAS
        - TP53
        - STK11 (enriched in 3+ group; p=0.01, lost significance after correction)

<u>Take Home Message</u>

- HER2 IHC 3+ is present in a clinically meaningful subset (~13%) of lung cancers and mostly in adenocarcinomas
- HER2 IHC does not reliably predict ERBB2 mutation or amplification.
- Cytology cell blocks (alcohol-prefixed) may under-call HER2 expression
    - Problem if have only cytology specimen
- Limitations
    - Did not look at clinical outcomes or data for T-DXd response
    - No FISH confirmation

4. **D'Ambrosio D, et al. Detection of targetable genetic alterations in SMARCA4-deficient neoplasms of the lung – further evidence of a relationship between SMARCA4-deficient undifferentiated tumor and non-small cell carcinoma. Human Pathology. 2026;167:106007.**

Background

Thoracic SMARCA4-deficient undifferentiated tumor (SMARCA4d-UT) is characterized by

- Loss of SMARCA4 (BRG1) expression
- Association with heavy smoking
- Aggressive clinical behavior with early nodal and distant metastasis
- Rhabdoid to epithelioid morphology with high-grade cytology
- Variable keratin expression
- Frequent loss of SMARCA2 (BRM)

Accumulating evidence suggests these tumors may represent high-grade transformation of non-small cell lung carcinoma (NSCLC).

- SMARCA4 alterations occur in 8–12% of NSCLC.
- Smoking-related mutational signatures are common.
- Coexistence of conventional NSCLC morphology within SMARCA4-deficient tumors.
- Similar survival between SMARCA4d-UT and SMARCA4-deficient NSCLC.

This study examines the clinicopathologic and molecular features of 18 SMARCA4-deficient lung tumors to further clarify this relationship

Methods

Case Selection: Retrospective review (2021–2025) of 18 SMARCA4-deficient lung neoplasms by 4 pathologists and classified by consensus

SMARCA4-deficient carcinoma:

- BRG1 loss
- Morphologic evidence of carcinoma (glandular/squamous architecture or mucin) **or** IHC evidence of differentiation (TTF-1, p40, CDX2)

SMARCA4d-UT:

- Exclusively undifferentiated rhabdoid/epithelioid morphology
- No morphologic carcinoma component
- TTF-1 and p40 negative
- Keratin-negative/patchy
- Supportive: SMARCA2 loss, Claudin-4 loss

IHC: **P**erformed as part of diagnostic evaluation

- See below

Molecular Testing: Performed in 10 cases from FFPE tissue

- Oncomine Focus (50 genes)
- GenomePACT (607-gene panel)
- FusionSEQer (103 fusion genes)

Results

Clinical Features

- 18 patients identified, 83% smokers
- Median follow-up: 7 months
    - No major survival difference between SMARCA4d-UT and SMARCA4-deficient carcinoma.

Histology Distribution:

- 13 Carcinomas: 11 adenocarcinomas, 1 squamous cell carcinoma, 1 poorly differentiated NSCLC
- Only 5 SMARCA4d-UT
- All carcinomas had identifiable undifferentiated components (adeno patterns, squamous diff)
- SMARCA4d-UT: sheets of pleomorphic rhabdoid/epithelioid cells, brisk mitoses, necrosis.

Immunophenotype/Molecular

- Observations
- Keratin: Focal/patchy in UTs, variable expression in carcinomas
- PD-L1: **HIGH**
    - Positive in 72%
    - TPS >50% in 67%
- Targetable Molecular Alterations were detected in 6/10 tested cases: 1 UT, rest were SMARCA4-AdCa
    - UT had a *EML4::ALK* mutation
    - Variety of gene fusions and point mutations (EGFR, KRAS, MAP2K1, SMARCA4).

Immunonphenotypic and molecular characteristics of all 18 cases.

Case	Diagnosis	Keratin	BRG-1	BRM	INI-1	TTF-1	PD-L1	Claudin-4	Gene Fusions	Point mutations
1	SMARCA4d-AdCa	Diffuse	Globally reduced	Lost	Retained	Neg	80 %	N/A	*BRAF::CHCHD3*	None detected
2	SMARCA4d-AdCa	Focal	Lost	Part. Lost	N/A	N/A	100 %	N/A	None detected	None detected
3	SMARCA4d-UT	Neg	Lost	Retained	Retained	N/A	80 %	N/A	*EML4:::ALK*	None detected
4	SMARCA4d-AdCa	Diffuse	Lost	Lost	Lost	Neg	90 %	N/A	None detected	None detected
5	SMARCA4d-UT	Patchy	Lost	N/A	N/A	Neg	80 %	N/A	None detected	KRAS c.34G > T p.G12C
6	SMARCA4d-AdCa	Patchy	Lost	N/A	Retained	Focal	0 %	N/A	*FGFR1::FILIP1*	None detected
7	SMARCA4d-UT	Focal	Lost	Retained	Retained	Neg	95 %	N/A	Not tested	Not tested
8	SMARCA4d-AdCa	N/A	Lost	N/A	Retained	Patchy	95 %	N/A	None detected	None detected
9	SMARCA4d-AdCa	N/A	Lost	N/A	N/A	Neg	40 %	N/A	None detected	*SMARCA4 p.E1312K and EGFR p. L747S*
10	SMARCA4d-AdCa	Diffuse	Lost	Lost	Retained	Focal	70 %	N/A	Not tested	Not tested
11	SMARCA4d-AdCa	Patchy	Lost	Part. Lost	Retained	Patchy	70 %	N/A	None detected	MAP2K1, c.171G > T, p.K57 N
12	SMARCA4d-AdCa	Patchy	Lost	Part. lost	N/A	Neg	0 %	N/A	Not tested	KRAS, c.183A > T, p.Q61H
13	SMARCA4d-NSCLC	Diffuse	Lost	N/A	N/A	Neg	0 %	N/A	Not tested	Not tested
14	SMARCA4d-SCC	Patchy	Lost	Retained	N/A	Neg	100 %	N/A	None detected	None detected
15	SMARCA4d-UT	Neg	Lost	Lost	N/A	Neg	0	N/A	Not tested	Not tested
16	SMARCA4d-AdCa	N/A	Lost	N/A	N/A	Patchy	0 %	N/A	Not tested	None detected
17	SMARCA4d-UT	Focal	Globally reduced	Retained	Retained	Neg	100 %	Neg	Not tested	Not tested
18	SMARCA4d-AdCa	Diffuse	Lost	Part. lost	N/A	Patchy	50 %	Pos	Not tested	EGFR L858R

Treatment Response

- 67% received immune checkpoint inhibitors with variable responses
    - Some complete/major pathologic responses
    - Several non-responders despite high PD-L1
- ALK-positive SMARCA4d-UT demonstrated durable targeted therapy response.

<u>Take Home Message:</u>

- SMARCA4-deficient lung carcinomas frequently harbor targetable alterations (EGFR, ALK, KRAS, MAP2K1) -> Still worth doing molecular
- High PD-L1 expression is common but response to immunotherapy is variable.
- Not sure if this data set really helps with corroborating suspicion that SMARCA4d-UTNs are a result of high grade transformation of prior NSCLC since they only had 5 and of those, only 2 were tested for molecular.

Articles for Notation

Editorials

Summary: Three editorials in *European Respiratory Journal* regarding Ryerson CJ, et al. Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement. Eur Respir J 2025; 66: 2500158

Homer RJ. Commentary on: Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement. Eur Respir J. 2026;67(1):2501947.

Summary of Critiques:

- The extent of fibrosis and secondary features should be incorporated, especially for hypersensitivity pneumonitis, for treatment purposes
- DIP/AMP and RB-ILD distinction split
- Problems with new classification for bronchiolocentric interstitial pneumonia
    - UIP can also show bronchocentricity, which can be a problem in cryobiopsies
    - Broncholectasis with mucostasis can also be seen in honeycombing
- Lack of guidance on reconciling discordant imaging and histology

Fraser A, Tsai LL, Fermoyle CC, et al. Do we need to prioritise interstitial lung disease clinical diagnoses? A comment on the 2025 interstitial pneumonia statement. Eur Respir J. 2026;67(1):2501987.

Summary of Critique:

- Felt pathology/radiology was OVER emphasized for diagnosis compared to clinical presentation in multidisciplinary review (MDR)
    - Other factors should be considered such as clinical features, exposure, serologies, radiology before histology
    - Felt this would alter treatment if morphology based

Nicholson AG, Adegunsoye A, Piciucchi S, et al. Reply: From the authors of the ERS/ATS statement on the international multidisciplinary classification of the interstitial pneumonias. Eur Respir J. 2026;67(1):2502271.

Summary of Reply:

- R/E Homer:
    - Fibrosis should be documented in biopsy but MDR with imaging is better assessment of extent of fibrosis
    - RB-ILD and AMP could be merged as smoking-related ILD in MDR but remain separate histologic patterns
    - Statement does not address cryobiopsies, pathologists should recognize bias in such biopsies
- R/E Fraser: Argues morphologic pattern and MDR are separate and to document first, but clinical context is the organizing principle

Neoplastic

Boland JM, Stetzik L, Roden AC, et al. Development of an Artificial Intelligence Model to Aid in Measurement of Invasion, Comprehensive Histologic Subtyping, and Grading of Pulmonary Adenocarcinoma. Modern Pathology. 2026;39(1):100923.

Summary:

- Development of AI model to assess invasive size in lepidic-predominant tumors and comprehensive histologic subtyping
    - 100 resected treatment naïve pulmonary adenocarcinomas-> 35 used for training and 65 for validation
- Used Aiforia for AI model creation, annotations by 6 pulmonary pathologists
- Manual assessment performed by 3 pulmonary pathologists
    - Tumor size
    - Invasive size
    - Histologic subtyping
- Results:
    - Small difference in size between manual and AI estimations for invasive size (<3 mm) and tumor size (<1.3 mm)
    - Difference in invasive percentage was <15.3%
    - Ranges were wide, with % pattern agreement decreasing in validation set
    - Agreement was moderate to substantial between AI and each observer for training set, but only moderate between AI and each observer in validation set
        - Agreement was better for IASLC grade than predominant pattern

Take-home message:

- Proof of concept study to use AI to aid in evaluating pulmonary adenocarcinoma size, histologic subtyping, and grade
    - Did better in evaluating size vs histologic type (especially acinar and lepidic pattern)
- While AI has moderate agreement, more training needs to be done with manual oversight

Pineda CM, Guan Z, Kwon H, Rangachari D, Costa DB, VanderLaan PA. A Comprehensive Mutational and Histopathological Analysis of STK11-Mutant Non–Small Cell Lung Carcinomas. Modern Pathology. 2026;39(1):100938.

Summary:

- *SKT11*-mutant NSCLCs are aggressive and have impaired response to ICIs and KRAS targeted therapies
- Study aimed to address knowledge gap by characterizing 139 *SKT11*-mutant non squamous NCSLCs: Genomic alterations, comutational profiles, histopathologic features, metastatic patterns, survival outcomes
- *SKT11* mutant tumors had overall
    - Higher rates of poorly differentiated tumors, aggressive histologic growth patterns, STATs, multifocality, LN mets
    - Higher rates of smokers, less Asian individuals
    - Higher frequency of brain mets, lower frequency of malignant pleural effusions
    - Higher TMBs, lower PD-L1 TPS
    - Worse survival outcomes- *STK11*-loss/*KRAS*-mutant cohort had worse survival probability
- Comutational profiles

- Lower frequencies of *ALK* fusions and *EGFR* mutations; higher *KRAS* and *SMARCA4* mutations
- *SKT11* missense mutants have higher TMPS and PD-L1 TPSs
- *SKT11* loss have highest comutation rates, lower PD-L1 TPS rates, highest rates of brain mets

Take-home message: *SKT11*-mutant NCSLCs have different mutation profiles that can affect survival rates and treatment options

Nakagomi T, Fujimoto M, Kuriyama S, et al. Genome-wide DNA methylation profiling of pleomorphic carcinoma of the lung. Human Pathology. 2026;167:106001.

Summary

- Study aimed to look at methylation profile of pleomorphic carcinoma of lung
  - Went by WHO classification: Poorly differentiated NSCLC containing ≥10% sarcomatoid component (spindle and/or giant cells)
- Sampled 11 completely surgically resected pleomorphic carcinomas (2011–2018)
  - Infinium MethylationEPIC BeadChip
  - 865,918 CpG sites initially; filtered to 732,793 CpG sites
- Specific promoter **hypomethylation** events in the sarcomatoid component correlate with aggressive behavior: LVI, higher stage, worse survival outcomes
- IHC validation of areas of interest: OCIAD2, COX6C, TSKU-> Increased in sarcomatoid components and correlated with worse outcome

Wu JY, Liang GZ, Chen TQ, Qiu HP, Huang CB, Xie XP. Prognostic comparison of lymph node metastasis subtypes in lung adenocarcinoma: clinical implications of intranodal metastasis versus extranodal extension for optimizing R classification. Lung Cancer. 2026;211:108876.

Summary:

- Study evaluated the prognostic significant of intranodal metastasis (INM) versus extranodal extension (ENE) in 357 patients with pT1 lung adenocarcinomas
- Both INM and ENE groups had worse OS and DFS and recurrence rates than N0 patients
- No statistically significant survival difference between INM and ENE.
- Adjuvant therapy rates were similar between INM and ENE groups (~55%), largely platinum-based chemotherapy.

Take-home message: INM and ENE both show worse survival rates-> Authors argue this can be seen as biologically significant residual disease

Brune MM, Roma L, Chijioke O, et al. MTAP Expression by Immunohistochemistry: A Novel Biomarker in NSCLC. Journal of Thoracic Oncology. 2026;21(1):112-123.

Summary:

- Study evaluated MTAP IHC loss in NSCLC as compared to NGS based detecting for CDKN2A copy number loss (FISH gold standard)
- MTAP deficiency important
  - Loss leads to accumulation of MTA-> effective for PRMT5 and MAT2A inhibitors
  - Emerging negative predictor to ICI response
- Found MTAP deficiency by IHC in 18.2% of NSCLC (698 cases). Only 28.4% MTAP-deficient tumors showed CDKN2A loss on NGS.

- Strong inverse correlation between MTAP loss and TP53 mutation

Take-home message:

- MTAP IHC can detect MTAP loss in NSCLC and is easier to perform and more reliable than CDKN2A-> Did not compare many to FISH
- Authors recommend evaluating at least 100 tumor cells, to look at cytoplasmic loss, and to have internal positive controls.
- Future would be to see if there are survival differences in MTAP IHC loss vs MTAP NGS loss only

Chen-Yost HI, Chapel DB, Hrycaj SM, et al. Immunohistochemical characterization of peritoneal inclusion cysts with squamous metaplasia. Histopathology. 2026;88(2):533-537.

Summary:

- To evaluate the IHC characteristics of PICs
- 10 PICs were identified, all had diffuse squamous metaplasia.
  - The suprabasal squamous epithelial portion had diffuse expression of claudin 4 and p63/p40, as well as co-expression of WT-1.
  - The basal layer had a mesothelial phenotype positive for WT1 and D2-40, but negative for claudin 4

Take-home message: PICs are benign entities with a unique biphenotypic IHC staining profile that may be confusing

Hashmi AA, et al. Lung Carcinoma Metastatic to the Breast: A Comprehensive Analysis of Clinical Presentation, Morphologic, and Molecular Features, With Emphasis on Diagnostic Pitfalls. Modern Pathology. 2026;39(1):100936.

Carillo AM, et al. A challenging case of enteric-type lung adenocarcinoma metastatic to the thyroid harboring RET-fusion diagnosed on fine-needle aspiration. Virchows Arch. 2025;487(6):1433-1438..

Summaries: Two articles describing metastatic lung carcinoma presenting in unusual locations- breast and thyroid- and the challenges that can arise with identification

Non-Neoplastic/Other

Borowitz MJ, Blackford AL, Nagelia S, Hruban RH. Large Language Models Can Generate High-Quality Pathology Multiple-Choice Questions Comparable With Questions Written by a Human Expert. Modern Pathology. 2026;39(1):100940.

Purpose: Evaluate the quality of LLM-generated pathology multiple-choice questions versus human generated questions

Results: Chat GPT generated questions were easier than human authored questions and had more poor/unacceptable questions. Gemini did better than ChatGPT. Human MCQs were overall more clinically realistic but sometimes tested trivial points.

Take home message: If you plan to use LLMs to generate MCQs, use it with caution

Reviews, Guidelines, and Consensus Statements

Antoniou KM, Distler O, Gheorghiu AM, et al. ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease. Eur Respir J. 2026;67(1):2402533.

Take-home message for pathologists:

- The ERS/EULAR does **not** recommend lung biopsy for CTD-ILD due to potential risks of biopsy (pneumothorax) and low diagnostic likelihood on biopsy
- BALs are recommended to rule out alternative diagnosis

Fang W, Detterbeck F, Ackman JB, et al. International Thymic Malignancy Interest Group Standard Definitions, Policies, and Reporting Measures for Thymic Epithelial Tumors. Journal of Thoracic Oncology. 2026;21(1):102-111.

Take-home message for pathologists:

- TNM-9 replaces Masoka-Koga stages
  - Stage I and II have similar prognostic outcomes
- Updates to the TNM classification
  - Phrenic nerve and lung invasion has been downstaged to T2
  - Mediastinal pleural invasion discarded as T indicator but should be listed as an "additional histologic descriptor" if identified. Surgeons should mark the mediastinal pleura on resection to help

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The January 2026 issue of Archives of Pathology & Laboratory Medicine celebrated the journal's 100th Anniversary with modern reflections on landmark papers

Churg A, Muller NL. Granulomatosis With Polyangiitis (Wegener Granulomatosis): Then and Now. Arch Pathol Lab Med. 2025 Dec 22;150(1):37-43

Ulbright TM. Concerning the Seminal Study of Anterior Mediastinal Teratomas by H. G. Schlumberger: An Update and Modern Contextualization. Arch Pathol Lab Med. 2025 Dec 22;150(1):27-36.