Pulmonary Pathology Journal Club
(Articles from February 2024)

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March 18, 2024

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3. Takam Kamga P, Mayenga M, Sebane L, Costantini A, Julie C, Capron C, Parent F, Seferian A, Guettier C, Emile JF, Giroux Leprieur E. Colony stimulating factor-1 (CSF-1) signalling is predictive of response to immune checkpoint inhibitors in advanced non-small cell lung cancer. Lung Cancer. 2024 Feb;188:107447.

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7. Pittaro A, Crivelli F, Orlando G, Napoli F, Zambelli V, Guerrera F, Sobrero S, Volante M, Righi L, Papotti M. Pulmonary Low Malignant Potential Adenocarcinoma: A Validation of the Proposed Criteria for This Novel Subtype. Am J Surg Pathol. 2024 Feb 1;48(2):204-211.

8. Kawamoto N, Mimae T, Tsutani Y, Kamigaichi A, Tsubokawa N, Miyata Y, Okada M. Tumor distance from the mediastinum predicts N2 upstaging in clinical stage I lower-lobe non-small cell lung cancer. J Thorac Cardiovasc Surg. 2024 Feb;167(2):488-497.e2.

Non-Neoplastic

1. Suryadevara R, Gregory A, Lu R, Xu Z, Masoomi A, Lutz SM, Berman S, Yun JH, Saferali A, Ryu MH, Moll M, Sin DD, Hersh CP, Silverman EK, Dy J, Pratte KA, Bowler RP, Castaldi PJ, Boueiz A; COPDGene investigators.

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2. Huang J, Lin Z, Lin J, Xie S, Xia S, Chen G, Zheng Z, Xu Z, Liu F, Wu H, Li S. Causal role of lipid metabolism in pulmonary alveolar proteinosis: an observational and mendelian randomisation study. Thorax. 2024 Jan 18;79(2):135-143.

3. Asakura T, Okuda K, Chen G, Dang H, Kato T, Mikami Y, Schworer SA, Gilmore RC, Radicioni G, Hawkins P, Barbosa Cardenas SM, Saito M, Cawley AM, De la Cruz G, Chua M, Alexis NE, Masugi Y, Noone PG, Ribeiro CMP, Kesimer M, Olivier KN, Hasegawa N, Randell SH, O'Neal WK, Boucher RC. Proximal and Distal Bronchioles Contribute to the Pathogenesis of Non-Cystic Fibrosis Bronchiectasis. Am J Respir Crit Care Med. 2024 Feb 15;209(4):374-389.

Reviews & Editorials

1. Bankier AA, MacMahon H, Colby T, Gevenois PA, Goo JM, Leung ANC, Lynch DA, Schaefer-Prokop CM, Tomiyama N, Travis WD, Verschakelen JA, White CS, Naidich DP. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology. 2024 Feb;310(2):e232558.

2. Borczuk AC. Pathogenesis of Pulmonary Long COVID-19. Mod Pathol. 2024 Feb;37(2):100378.

3. Kerr KM, Bubendorf L, Lopez-Rios F, Khalil F, Roy-Chowdhuri S, Joubert P, Hartmann A, Guerini-Rocco E, Yatabe Y, Hofman P, Cooper WA, Dacic S. Optimizing tissue stewardship in non-small cell lung cancer to support molecular characterization and treatment selection: statement from a working group of thoracic pathologists. Histopathology. 2024 Feb;84(3):429-439.

Case Reports & Letters to the Editor

1. Monteagudo C, Pérez-Debén S, Pérez-Roda I, Giner F, Machado I. CD34-negative, STAT6-negative, Low-grade, Low-risk Solitary Fibrous Tumor. Am J Surg Pathol. 2024 Feb 1;48(2):247-249.

2. Wang S, Dai H. Crazy-Paving Pattern in Pulmonary Sarcoidosis. N Engl J Med. 2024 Feb 29;390(9):e21.

3. Liao SY, Maier LA, Fingerlin TE. Genome and Transcriptome-Wide Association Study of Fibrotic Sarcoidosis in European Americans. Am J Respir Crit Care Med. 2024 Feb 1;209(3):334-337.

4. Ogimoto A, Katsurada N, Yatani A, Mimura C, Yamamoto M, Tachihara M. HIP1-ALK-Rearranged Lung Cancer in a Young Adult With BRAF V600E

Mutation Detected After ALK Tyrosine Kinase Inhibitor Therapy: A Case Report. JTO Clin Res Rep. 2023 Nov 25;5(1):100612.

5. Jeganathan N, Sathananthan M. Interstitial Lung Disease Cases, Prevalence Rates and Trends Among States in the United States. Chest. 2024 Feb;165(2):389-395.

6. Lynn E, Forde SH, Franciosi AN, Bendstrup E, Veltkamp M, Wind AE, Van Moorsel CHM, Lund TK, Durheim MT, Peeters EFHI, Keane MP, McCarthy C; and Northern European LAM Prevalence Consortium. Updated Prevalence of Lymphangioleiomyomatosis in Europe. Am J Respir Crit Care Med. 2024 Feb 15;209(4):456-459.

7. Haddad E, Bottet B, Thiebaut PA, Morin S, Dreyfus H, Vannier É, Vincent C, Marguet F, Lamy A, Sobol H, Baste JM, Guisier F, Sabourin JC, Piton N. Squamous Cell Carcinoma of the Lung With Microsatellite Instability in a Patient With Lynch Syndrome: A Case Report. JTO Clin Res Rep. 2023 Oct 19;5(1):100595.

8. Sugimoto A, Hirata M, Jinnouchi K, Ohata K, Kikuchi R, Haga H, Yoshizawa A. A case of stratified bronchiolar adenoma with immunofluorescence analysis: comments on "Frequent EGFR exon 20 insertion in the so-called peripheral type squamous cell neoplasm of uncertain malignant potential: a variant of bronchiolar adenoma or under-recognized entity?". Histopathology. 2024 Feb;84(3):570-573.

ARTICLES FOR DISCUSSION

1. **Chiang CL, Huang HC, Luo YH, Shen CI, Chao HS, Tseng YH, Chou TY, Schrump DS, Yeh YC, Chen YM. Clinical utility of immunohistochemical subtyping in patients with small cell lung cancer. Lung Cancer. 2024 Feb;188:107473.**

Purpose:
Molecular subtyping of small cell lung cancer (SCLC) tumors based on the expression of four transcription factors (ASCL1, NEUROD1, POU2F3, and YAP1) using immunohistochemical (IHC) staining has recently emerged as a proposed classification approach. This study examined this subtyping method in Asian patients with SCLC and investigated its correlation with treatment efficacy in terms of progression-free survival (PFS).

Methods:
- *72 tumor samples were gathered from patients with SCLC.*
- *Levels of the four transcription factors were measured with IHC staining and subtypes were defined based on relative expression levels.*
- *Treatment response to combined chemotherapy/immunotherapy (n = 22) was assessed.*

Results:
- *ASCL1 was the most common subtype (55.2% of samples), followed by NEUROD1 (26.9%) and POU2F3 (9%). No tumors exhibited predominant YAP1 positivity.*
- *41.8% of tumors demonstrated positivity for two subtype markers.*
- *Half of tumors switched subtype after disease progression (n = 12).*
- *Non-ASCL1/NEUROD1 subtypes (elsewhere referred to as an "inflamed immunophenotype") had PFS similar to ASCL1/NEUROD1 subtypes.*
- *SCLC tumors transformed from EGFR-mutant precursor tumors responded less well to treatment than de novo SCLC.*

Take home points:
- *Characterizing SCLC with IHC is challenging because:*
  - *Subtypes are often coexpressed, and*
  - *Tumors frequently switch subtypes during disease progression.*
- *RNA expression analysis still seems to remain the gold standard for SCLC subtyping, but perhaps IHC information could still be useful in some circumstances.*
- *Further investigation, especially with larger cohort sizes, is warranted.*

2. **Haragan A, Parashar P, Bury D, Cross G, Gosney JR. Machine-learning-based image analysis algorithms improve interpathologist concordance when scoring PD-L1 expression in non-small-cell lung cancer. J Clin Pathol. 2024 Jan 18;77(2):140-144.**

Purpose:

To explore whether the use of machine learning-derived image analysis tools can improve interpathologist concordance in assessing PD_L1 expression in NSCLC and thereby improve consistency of interpretation.

Methods:

- 13 biopsy specimens of NSCLC (7 adenocarcinomas and 6 squamous cell carcinomas) were selected to represent a range of PD-L1 (SP263 clone) expression levels
- uPath PD-L1 image analysis + Roche Navify DP
- 5 pathologists independently scored PD-L1 using the image analysis algorithm (after training in this platform)
- After 6-week washout, they rescored without image analysis software (using Ventana interpretation guide)
- Tumor Proportion Score (TPS) was placed in 1 of 3 categories: negative (<1%), weak positive (1-49%), positive (>50%); continuous results (%s) also captured

Results:

- Agreement was “very good” (kappa .886) using image analysis vs “good” (kappa 0.613) without image analysis with respect to categorical reporting.
- Agreement was “excellent” (Intraclass coefficient correlation 0.954) using image analysis and “good” (ICC 0.837) without imaging analysis for absolute (continuous) reporting.
- Pathologists noted that ROI selection was very subjective
- Pathologists mostly liked the software to confirm or question their own assessments (as a QC tool).

Take home points:

- Even though the 5 pathologists had a “lot” of PD-L1 experience, the image analysis software improved concordance.
- The most marked improvement in consistency was in the palcment of cases into the three categories of ‘negative,’ ‘weak positive,’ and ‘strong positive.’
- They believe further training would improve selection of ROI
- Most value comes when there are multiple small pieces that cannot be viewed simultaneously
- Image anaylsis should not be applied blindly (or without human oversight)
- Unclear if this increased concordance translates to improved accuracy
- No clinical follow-up with this study

3. **Smith ML, Mino-Kenudson M, Butterfield RJ, Dacic S, Colby TV, Churg A, Beasley MB, Hariri LP. Pulmonary Pathology Society Survey on Practice Approaches in the Histologic Diagnosis of Fibrotic Interstitial Lung Disease: Consensus and Opportunities. Arch Pathol Lab Med. 2024 Feb 1;148(2):168-177.**

Purpose:
The Pulmonary Pathology Society (PPS) ILD working group sought to survey current practice approaches on the histologic diagnosis of UIP and other fibrotic ILD to identify areas of consistency and consensus, and to reveal practice approaches and areas of lack of consensus within the pulmonary pathology community. Identification of areas with a lack of consensus provides direction for future pathologic study of fibrotic ILD, for further clarification of diagnostic criteria and reporting terminology.

Methods:
- *A 20-minute survey was devised with 5 subsections in the following categories:*
    - *Background information – to enable subgroup analysis based on practice setting, fellowship training, performance of outside consultation, experience, and region of practice.*
    - *Histologic guidelines*
    - *Use of clinical and radiologic information*
    - *Diagnostic line terminology*
    - *Specific histologic features including:*
        - *UIP in IPF*
        - *Airway centered fibrosis (ACF)/peribronchiolar metaplasia (PBM)/giant cells/granulomas*
        - *Connective tissue disease (CTD)*
        - *Acute lung injury*
        - *Other superimposed diseases*
- *The survey was available for 78 days, closed on February 1, 2022, and sent to 220 active PPS members.*
- *Basic descriptive statistics were used for the full analysis.*
- ***x^2** test used to compare survey response items by respondent subgroups:*
    - *Years of practice (0-10, 11-20, and >20 years)*
    - *Region of practice (North America, Europe, all other regions)*
    - *Pulmonary pathology fellowship training (present or absent)*
    - *Receipt of ILD consultation cases (present and absent)*
- *Hypothesis testing by Bonferroni correction, Analysis performed in SAS version 9.4.*

Results:
- *161 completed surveys returned (78% of the 220 active members)*
- *89% reported using published histologic features in clinical guidelines for idiopathic pulmonary fibrosis (IPF) in their pathologic diagnosis.*

- *Variability in reporting terminology, quantity and quality of histologic features, and use of guideline categorization*
- *Respondents were likely to have access to pulmonary pathology colleagues (79%), pulmonologists (98%), and radiologists (94%) to discuss cases, but only about half of responders reported that additional clinical or radiologic history may alter their pathologic interpretation.*
- *Airway-centered fibrosis, granulomas, and types of inflammatory infiltrates were considered important, but there was poor agreement on how these features are defined.*
- *Diagnostic Line Terminology for UIP:*
    - *UIP with a comment (n = 44, 27%), UIP pattern (n = 39, 24%), advanced fibrosing interstitial pneumonia consistent with UIP pattern (n = 35, 22%), and advanced fibrosing interstitial pneumonia consistent with UIP (n = 16, 10%).*
    - *74 responders (46%) use the term UIP pattern, whereas 83 (51%) use the term UIP*
    - *Most (n = 90, 56%) prefer a descriptive diagnosis for cases of fibrosing interstitial pneumonia without all features of histologic UIP, but UIP considered the leading diagnosis.*
    - *Most (n = 135, 84%) agree that histologic UIP is a useful pathologic term, and 151 (94%) agree UIP is a pattern of injury seen in several fibroinflammatory diseases*
- *Diagnostic Histologic Features for Different Entities:*
    - *UIP*
        - *Most (n = 148, 92%) agree that fibroblastic foci (FFs) may be seen in ILD other than UIP, and 127 (79%) report that FFs are required for a histologic diagnosis of UIP.*
        - *102 (63%) and 99 (62%) allow mild interstitial fibrotic expansion and mild chronic inflammation in histologic UIP, respectively*
        - *Significance of and recognition of honeycomb change variable*
    - *Hypersensitivity pneumonitis features and airway centered fibrosis (ACF)*
        - *Most respondents believe ACF exists, and consider chronic inhalational disease when encountered.*
        - *Only 42% report that it is easy to recognize ACF.*
        - *Significant agreement regarding the significance of granulomas*
        - *Disagreement regarding the significance of giant cells in a diagnosis of UIP*
        - *131 (81%) report that extensive PBM and mucostasis alone favors inhalational etiologies, but 91 (57%) agree these features are also seen in UIP and a minority of 60 (37%) report that this does not influence their diagnosis of UIP.*
    - *CTD Associated ILD*
        - *Agreement that prominent lymphoid hyperplasia, lymphoid follicles, chronic pleuritis, and cellular inflammatory infiltrates*

away from areas of honeycombing suggests a non-IPF diagnosis.
        - *Lack of agreement on the clarity of these features, and the extent at which they require to be considered significant.*
    - *Diseases Superimposed on Fibrotic ILDs*
        - *UIP with superimposed acute lung injury most commonly reported as "acute lung injury (organizing pneumonia [OP], diffuse alveolar damage [DAD], acute fibrinous and organizing pneumonia [AFOP]) with background UIP" (n = 90, 56%), followed by "acute on chronic fibrosing ILD and explain the differential diagnosis" (n = 52, 32%)*
        - *Over half agree cicatricial OP is an ILD, and 43% find difficult to distinguish from UIP*
        - *Smoking-related ILD: (45%) agree advanced fibrosis and FFs should not be seen in smoking-related ILD, and 70 (44%) agree HC lung should not be seen.*
- *Subset analysis:*
    - *Respondents who received consultation cases were:*
        - *More likely to work in academic centers, share ILD cases with colleagues, and to have a formal MDD at their institutions*
        - *More likely to provide descriptive diagnosis with cases without all features of UIP, but UIP was the preferred diagnosis.*
        - *More likely to consider ACF significant when there were associated granulomas.*
        - *More likely to feel less confident in the clarity of the definition of cellular inflammatory infiltrates away from honeycomb areas.*
        - *Less likely to agree that fibrosing OP can result in advanced fibrosis similar to UIP.*
    - *Experience: Those with more years of practice were more likely to agree that HC lung should not be seen in smoking related ILD*
    - *Regional variance:*
        - *North American pathologists more likely to alter their pathologic diagnosis based on clinical and radiologic information.*
        - *North American and European pathologists have more pulmonary pathology colleagues than in other regions.*
        - *Pathologists in North America are more likely to agree that the amount of chronic pleuritis needed to consider diagnoses other than UIP is not clear.*
    - *Fellowship training:*
        - *Reported in 69 respondents (45%)*
        - *Associated with smaller practices, and more likely to receive consultation cases.*
        - *Less likely to agree that the pattern of fibrosis in which they encounter fibroblastic foci changes their impression of the*

significance of the fibroblastic foci (50 [73%] versus 77 [92%]) (P = .006)

- *More likely to report cases with acute lung injury and UIP as "acute lung injury with background UIP" (P = .01)*

Take home points:

- *Most agree that UIP is a useful pathologic term (n = 135, 84%), but the survey highlights a lack of consistency regarding how cases that meet criteria for UIP are reported, with 74 responders (46%) using UIP pattern terminology and 83 (51%) using UIP.*
- *There is significant variability in how cases of UIP secondary to another cause are reported, highlighting a need for clarity and consensus on diagnostic line terminology.*
- *Clarity on how and when to incorporate clinical and radiology findings into pathology diagnosis may lead to more standardized pathologist reporting*
- *Lack of clarity regarding the quantity and quality of histologic features that suggest UIP secondary to an alternative etiology or diagnosis.*
    - *HC lung, granulomas, giant cells, ACF, PBM, lymphoid hyperplasia, lymphoid follicles, interstitial infiltrates, and chronic pleuritis need better definitions and clarification.*
- *Inconsistent data regarding the perception of advanced pulmonary fibrosis secondary to smoking-related ILD, fibrosing OP, and aspiration.*
- *Lack of guidelines in regard to cryobiopsy sampling may require modifications to diagnostic criteria.*
- *Role of genomic classifier testing in the workup of patients with suspected fibrotic ILD still uncertain.*
- *dDevelopment of a standardized atlas of histologic features in ILD for reference when assessing individual cases may be of benefit.*

4. **Nakagiri T, Amatya VJ, Kushitani K, Kambara T, Aoe K, Endo I, Miyata Y, Okada M, Takeshima Y. SPARC Is a Novel Positive Immunohistochemical Marker of Epithelioid Mesothelioma to Differentiate It From Lung Adenocarcinoma and/or Squamous Cell Carcinoma. Am J Surg Pathol. 2024 Feb 1;48(2):140-149.**

Purpose:
To identify a common positive mesothelioma marker to differentiate it from both lung adenocarcinoma and squamous cell carcinoma using gene expression data of mesothelioma and non-small cell lung cancer cell lines in cancer-dependency map.

Methods:
- 35 mesothelioma cell lines (20 epithelioid, 7 biphasic, 3 sarcomatoid and 5 uknown), 83 lung adenocarcinoma cell lines and 32 lung squamous cell lines
- Gene expression levels were compared using 2-class comparison
- IHC staining for TTF-1, Napsin A, p40, caltretinin, D2-40, and SPARC (cytoplasmic staining): 0(none), 1+(10%), 2+(10-50%), 3+(>50%)

Results:
- 168 genes differentiated SqCC from meso; 257 differentiating meso from AdenoCA+SqCC. SPARC gene had largest effect size (meso vs. any of others)
- SPARC was reactive in mesothelioma cells, not adenoCA or SqCC.
- Endothlial cells, fibroblasts and macorphages were diffusely positive and were a positive control.
- 42/45 (93%) epithleioid meso were SPARC+ (32 being 3+). SPARC was 2+ in two (5%) lung adenocarcinoma and 1+ in 2 (5%) SqCC
- Didn't report TTF-1/p40, but presumably they were all positive in adenoCA and SqCC (respectively) since they were "used to select."
- Meso vs solid lung adenoCA: diagnostic accuracy: SPARC (94%), Calretinin (91%), D2-40 (95%), WT1 (93%)
- Meso vs. SqCC: diagnostic accuracy: SPARC (94%), Calretinin (78%), D2-40 (63%), WT1 (93%)
- Meso vs SqCC+AdenoCA: SPARC (95%), calretinin (79%), D2-40 (73%), WT-1 (95%)

Take home points:
- Meso markers with high sensitivity and specificity don't exist to differentiate from SqCC
- CK5/6, calretinin and D2-40 have low specificity and WT1 has low sensitivity for differentiating meso from SqCC
- SPARC joins the growing list fo DAB2, Intelectin-1, glypican-1 and SOX6 as meso markers
- Immunohistochemistry showed that the sensitivity and specificity of SPARC for differentiating solid epithelioid mesotheliomas from solid lung adenocarcinoma and poorly differentiated lung squamous cell carcinoma were 93.3% and 95.2%, respectively
- The diagnostic accuracy of SPARC was the highest among the mesothelial markers for differentiating solid epithelioid mesothelioma from poorly differentiated lung squamous cell carcinoma with both high sensitivity and specificity.

ARTICLES FOR NOTATION

Neoplastic

1. Caldwell NJ, Ackman JB, Chebib I, Mino-Kenudson M, Nielsen GP, Hung YP. Anastomosing haemangioma of the mediastinum: Clinicopathological series with radiological and genetic characterisation. Histopathology. 2024 Feb;84(3):463-472.

   Purpose:
   Over 100 anastomosing hemangiomas (AH) have been reported, but most are in the abdominal/paraspinal region and mediastinal lesions of this type are rare. This group reports the clinicopathological, radiological and molecular characteristics of the largest single-institutional series of mediastinal AH. Seven patients were identified from 2011-2023: clinical, radiologic, and histopathologic evaluation, as well as targeted DNA-based NGS in five cases, was performed.

   Take home points:
   - Especially in small biopsies, AH can be a mimic of well-differentiated angiosarcomas: beware!
   - Radiologically, these lesions sometimes can be differentiated by PET or dynamic contrast-enhanced MRI, but standard CT imaging seems to be less helpful.
   - Short of genetic analysis (by which AH have been known to harbor hot-spot mutations in GNA family genes in a “quiet genome background”), careful H&E evaluation still seems to be the best way of avoiding diagnostic pitfalls.

2. Stockhammer P, Grant M, Wurtz A, Foggetti G, Expósito F, Gu J, Zhao H, Choi J, Chung S, Li F, Walther Z, Dietz J, Duffield E, Gettinger S, Politi K, Goldberg SB. Co-Occurring Alterations in Multiple Tumor Suppressor Genes Are Associated With Worse Outcomes in Patients With EGFR-Mutant Lung Cancer. J Thorac Oncol. 2024 Feb;19(2):240-251.

   Purpose:
   To investigate the clinical consequences of TSG alterations in patients with EGFR-mutant NSCLC treated with *EGFR* TKIs to determine whether additional TSG (*RB1*, *NF1*, *ARID1A*, *BRCA1*, and *PTEN*) alterations affect outcomes in the context of TP53 mutation status.

   Take home points:
   - Patients with TP53 + TSG mutations are a unique subgroup characterized by an aggressive disease phenotype and inferior outcomes on EGFR TKIs, pretty much regardless of therapy.

3. Takam Kamga P, Mayenga M, Sebane L, Costantini A, Julie C, Capron C, Parent F, Seferian A, Guettier C, Emile JF, Giroux Leprieur E. Colony stimulating factor-1 (CSF-1) signalling is predictive of response to immune checkpoint inhibitors in advanced non-small cell lung cancer. Lung Cancer. 2024 Feb;188:107447.

   Purpose:
   To assess the influence of the expression levels of tumor associate macrophages (TAMs)-related, via CSF-1 and IL-34 plasma levels, on tumor response in patients with advanced NSCLC receiving first-line ICIs therapy.

   Take home points:
   - High CSF-1 plasma levels at initial assessment associated with disease progression regardless of treatment.
   - High CSF-1 levels associated with shorted progression-free survival and overall survival in patients getting ICI therapy, but not in those receiving chemotherapy
   - No correlation seen in IL-34, CSF-1, CD163 and therapeutic response
   - CSF-1 may create a systemic immunosuppressive state that interferes with ICI therapy.

4. **Chong AL, Thorner P, Ellis M, Swensen J, Benlimame N, Fiset PO, Gatalica Z, Evans MG, Foulkes WD. Fetal Type Morphologies Suggest the Presence of DICER1 Hotspot Mutations in Non-small Cell Lung Cancer. Am J Surg Pathol. 2024 Feb 1;48(2):221-229. doi: 10.1097/PAS.0000000000002162. Epub 2023 Dec 5.**

   Purpose:
   DICER1 germline and somatic pathogenic variants (PV) are associated with pleuropulmonary blastoma (PPB), well-differentiated fetal lung adenocarcinoma (WDFLAC), and pulmonary blastoma (PB), but the role of DICER1 PVs in NSCLC is unknown. This study sought to examine the spectrum and prevalence of DICER1 PVs in NSCLC, and to compare the mutational landscape and histologic findings in cases with and without hotspot mutations.

   Take home points:
   - *235 of 12,146 NSCLCs (1.9%) showed ≥ 1 DICER1 PVs, including 9 with hotspot mutations.*
   - *All DICER1 hotspot-positive cases (except one from a small biopsy) showed features of PB/WDFLAC by histology.*
   - *DICER1 hotspot-positive cases had a strong co-occurrence of CTNNB1 and APC mutations compared to those without hotspot mutations, and most showed positive nuclear staining with beta-catenin IHC, suggesting a possible synergistic relationship between DICER1 hotspot PVs and activation of the WNT signalling pathway.*

- *DICER1 hotspot-negative NSCLC cases had a typical NSCLC mutational landscape and were not associated with fetal morphology.*
- *If morphologic features of PB and WDFLAC are present in NSCLC, genetic testing for DICER1 variants should be performed. If positive, genetic counseling should be considered.*

5. Dacic S, Cao X, Bota-Rabassedas N, Sanchez-Espiridion B, Berezowska S, Han Y, Chung JH, Beasley MB, Dongmei L, Hwang D, Mino-Kenudson M, Minami Y, Papotti M, Rekhtman N, Roden AC, Thunnissen E, Tsao MS, Yatabe Y, Yoshida A, Wang L, Hartman DJ, Jerome JA, Kadara H, Chou TY, Wistuba II; IASLC Pathology Committee. Genomic Staging of Multifocal Lung Squamous Cell Carcinomas Is Independent of the Comprehensive Morphologic Assessment. J Thorac Oncol. 2024 Feb;19(2):273-284.

   Purpose:
   To assess the clonal relationships between multifocal LSCC, using histologic vs. genomic assessments.

   Take home points:
   - A panel of 16 experienced thoracic pathologists had only “fair” agreement with a comprehensive histologic approach to distinguish separate primary tumors from IPM of multifocal SqCC. “Good” agreement was seen with adenocarcinoma.
   - Comprehensive genomic analysis should be adopted for staging of multifocal Lung Sq Cell Carcinomas.

6. **Burns L, Tukachinsky H, Raskina K, Huang RSP, Schrock AB, Sands J, Kulke MH, Oxnard GR, Tapan U. Real-World comprehensive genomic profiling data for diagnostic clarity in pulmonary Large-Cell neuroendocrine carcinoma. Lung Cancer. 2024 Feb;188:107454.**

   Purpose:
   Large cell neuroendocrine carcinoma (LCNEC) represents a heterogenous group of neuroendocrine neoplasms that has been shown to harbor distinct genomic subtypes resembling small cell lung carcinoma (SCLC), non-small cell lung carcinoma (NSCLC), and carcinoid tumors. This study sought to better define the NSCLC subtype to aid in establishing more tailored treatment protocols.

   Take home points:
   - *1,426 tissue samples of LCNEC evaluated and demonstrated a distribution of subtypes as follows: 39% SCLC-like, 37% NSCLC-like, 2% carcinoid like, and 22% unclassified.*
   - *NSCLC-like class-defining genomic alterations included SMARCA4, KRAS, FGF3/4/19, STK11, CDKN2A/B, MTAP and CCND1.*

- *Among the NSCLC-like group, 38% showed driver mutations; 5% of cases had a potentially actionable non-KRAS driver, 9% harbored KRAS G12C, and 3.6% harbored KRAS G12D mutation.*
- *Driver mutations were less common in the SCLC-like group.*
- *Circulating tumor fractions differed across LCNEC subtypes, with the SCLC category showing a higher tumor fraction (median 50%) than the NSCLC-like subcategory (median 8%), p = 0.026.*
- *Comprehensive genomic profiling in LCNEC is important as NSCLC-like LCNEC may respond to targeted therapies.*

7. Pittaro A, Crivelli F, Orlando G, Napoli F, Zambelli V, Guerrera F, Sobrero S, Volante M, Righi L, Papotti M. Pulmonary Low Malignant Potential Adenocarcinoma: A Validation of the Proposed Criteria for This Novel Subtype. Am J Surg Pathol. 2024 Feb 1;48(2):204-211.

   Purpose:
   To validate ≤3 cm size, nonmucinous histotype, ≥15% lepidic growth, and no ≥10% cribriform, ≥5% micropapillary, ≥5% solid), >1 mitosis per 2 mm^2, necrosis, vascular or visceral pleural invasion and STAS in a series of stage 1A resected adenoCA from 2 academic hospitals.

   Take home points:
   - This subgroup of patients does exist “in the wild”
   - Morphologic criteria for LMP-ADC supported by ancillary techniques represent a valid tool to better define this novel subgroup and to refine the stratification of invasive lung ADC, possibly suggesting modified follow-up protocols, based on the observed indolent behavior in most cases.

8. Kawamoto N, Mimae T, Tsutani Y, Kamigaichi A, Tsubokawa N, Miyata Y, Okada M. Tumor distance from the mediastinum predicts N2 upstaging in clinical stage I lower-lobe non-small cell lung cancer. J Thorac Cardiovasc Surg. 2024 Feb;167(2):488-497.e2.

   Purpose:
   To determine the association between the distance from the mediastinum to the tumor and the frequency of occult mediastinal nodal metastasis (OMNM) in patients with clinical stage I lower-lobe non–small cell lung cancer (NSCLC)

   Take home points:
   - The frequency of OMNM was significantly higher in patients with clinical stage I radiological pure-solid lower-lobe NSCLC of the inner-type than in those with outer-type NSCLC.
   - Tumor distance appeared to be the most important predictor of OMNMin patients with lower lobe NSCLC

Non-neoplastic

1. **Suryadevara R, Gregory A, Lu R, Xu Z, Masoomi A, Lutz SM, Berman S, Yun JH, Saferali A, Ryu MH, Moll M, Sin DD, Hersh CP, Silverman EK, Dy J, Pratte KA, Bowler RP, Castaldi PJ, Boueiz A; COPDGene investigators. Blood-based Transcriptomic and Proteomic Biomarkers of Emphysema. Am J Respir Crit Care Med. 2024 Feb 1;209(3):273-287.**

   Purpose:
   This study sought to discover blood omics biomarkers for chest computed tomography–quantified emphysema and develop predictive biomarker panels. It is hoped that identifying blood-based biomarkers of emphysema will facilitate early diagnosis and development of targeted therapies.

   Take home points:

- Totals of 3,829 genes, 942 isoforms, 260 exons, and 714 proteins were significantly associated with emphysema (false discovery rate, 5%) and yielded 11 biological pathways.
- Seventy-four percent of these genes and 62% of these proteins showed mediation by low body mass index (BMI).
- Prediction models demonstrated reasonable predictive performance in both COPDGene and ECLIPSE. The highest-performing model used clinical, blood cell, and protein data (area under the receiver operating characteristic curve in COPDGene testing, 0.90; 95% confidence interval, 0.85–0.90).

2. **Huang J, Lin Z, Lin J, Xie S, Xia S, Chen G, Zheng Z, Xu Z, Liu F, Wu H, Li S. Causal role of lipid metabolism in pulmonary alveolar proteinosis: an observational and mendelian randomisation study. Thorax. 2024 Jan 18;79(2):135-143.**

Purpose:
To elucidate the causal effect of lipid profiles on PAP using a large observational patient cohort and MR analysis and to identify potential mediating factors and drug targets.

Take home points:

- Lipid and metabolism-related traits play a crucial role in PAP risk
- Lipid-related mechanisms are a promising drug target to investigate for treating PAP

3. **Asakura T, Okuda K, Chen G, Dang H, Kato T, Mikami Y, Schworer SA, Gilmore RC, Radicioni G, Hawkins P, Barbosa Cardenas SM, Saito M, Cawley AM, De la Cruz G, Chua M, Alexis NE, Masugi Y, Noone PG, Ribeiro CMP, Kesimer M, Olivier KN, Hasegawa N, Randell SH, O'Neal WK, Boucher RC. Proximal and Distal Bronchioles Contribute to the Pathogenesis of Non-Cystic Fibrosis Bronchiectasis. Am J Respir Crit Care Med. 2024 Feb 15;209(4):374-389.**

Purpose:
To evaluate the role of non-cystic fibrosis bronchiectasis (NCFB) in bronchiolar disease manifest by mucus plugging and ectasia.

Take home points:
- NCFB exhibits distinctive proximal and distal bronchiolar disease.
- Both bronchiolar regions exhibit bronchiolar secretory cell features and mucus plugging but differ in mucin gene regulation and ectasia.

REVIEWS

1. **Bankier AA, MacMahon H, Colby T, Gevenois PA, Goo JM, Leung ANC, Lynch DA, Schaefer-Prokop CM, Tomiyama N, Travis WD, Verschakelen JA, White CS, Naidich DP. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology. 2024 Feb;310(2):e232558.**

   Summary:
   Fantastic summary meant to establish standardization of terminology for thoracic radiology and, thereby, to facilitate communications between radiologists and other clinicians. It has tons of images in it and every pulmonary pathologist should have this at their finger tips. Great document for pulmonary pathologists-in-training.

2. **Borczuk AC. Pathogenesis of Pulmonary Long COVID-19. Mod Pathol. 2024 Feb;37(2):100378.**

   Summary:
   Very nice review of the pathogenesis and pathology of pulmonary long COVID-19. Dr. Borczuk reviews the acute and subacute phases of the disease and then goes on to talk about the differences in what is observed in the cases of long COVID. In his experience OP, airway remodeling and organizing DAD were observed (similar to that in acute/subacute) but just associated with a course >4 weeks. This is likely associated with poor viral clearance, possibly owing to immunosuppression.

3. **Kerr KM, Bubendorf L, Lopez-Rios F, Khalil F, Roy-Chowdhuri S, Joubert P, Hartmann A, Guerini-Rocco E, Yatabe Y, Hofman P, Cooper WA, Dacic S. Optimizing tissue stewardship in non-small cell lung cancer to support molecular characterization and treatment selection: statement from a working group of thoracic pathologists. Histopathology. 2024 Feb;84(3):429-439.**

Summary:
A group of thoracic pathologists recommend factors to consider for optimal tissue management in the setting of NSCLC. Starting from when lung cancer is first suspected, keeping predictive biomarker testing in the front of the mind should drive the development of practices and procedures that conserve tissue appropriately to support molecular characterization and treatment selection.