Pulmonary Journal Club

May 2023 (April articles)

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Reviews, Editorials, Case Reports and Brief Reports (Listed here only, PDFs can be found in the folder)

Diep R, MacDonald MM, Cooper R, et al. Biopsy Method and Needle Size on Success of Next-Generation Sequencing in NSCLC: A Brief Report. J Thorac Oncol Clin Res Reports 2023;4(4):100497.

Friedman Flack K, Katzen J. Revealing the Rare: Pulmonary Fibrosis From Surfactant-Related Gene Mutation. Chest 2023; 163(4):744-745.

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Huyuk M, Fiocco M, Postmus PE, et al. Systematic review and meta-analysis of the prognostic impact of lymph node micrometastasis and isolated tumour cells in patients with stage I–IIIA non-small cell lung cancer Histopathol 2023;82:650-63.

Kirbis IS, Kholova I. Comments to: Nationwide differences in cytology fixation and processing methods and their impact on interlaboratory variation in PD-L1 positivity Virchows Archiv 2023;482:797-98.

Maniar R, Loehrer PJ. Understanding the landscape of immunotherapy in thymic epithelial tumors. Cancer 2023;129:1162-1172.

Osarogiabon RU, Schil PV, Giroux DJ, et al. The International Association for the Study of LunCancer Lung Cancer Staging Project: Overview of Challenges and Opportunities in Revising the Nodal Classification of Lung Cancer J Thorac Oncol 2023;18(4):410-418.

Perry WR, McHugh JB, Konopka K. Primary mesenchymal chondrosarcoma of the lung. Pathol Int 2023;73:170-72.

Sun TY, Nguyen B, Chen SB, et al. Brief Report: High Levels of CD47 Expression in Thymic Epithelial Tumors. J Thorac Oncol Clin Res Reports 2023;4(4):100498.

Lymphoid Interstitial Pneumonia (LIP) Revisited A Critical Reappraisal of the Histologic Spectrum of "Radiologic "and "Pathologic" LIP in the Context of Diffuse Benign Lymphoid Proliferations of the Lung.
Fraune et al. Am J Surg Pathol 2023;47:281–295 *Discussed by Julia Naso*

Background: The 2013 ATS/ERS consensus update specified histopathologic and radiologic criteria for lymphoid interstitial pneumonia (LIP), but use of the term LIP in practice is variable and the clinical utility of this term is questioned.

- ATS/ERS Pathologic LIP: diffuse interstitial lymphocytes/plasma cells/macrophages, absent or inconspicuous OP, no necrotizing granulomas, no light chain restriction or lymphatic tracking
- ATS/ERS Radiologic LIP: Striking cyst formation in some cases

Aim: To compare cases meeting the pathologic criteria for LIP with those meeting the radiologic criteria for LIP, and assess clinical correlates of these entities

Methods: A multiinstitutional collection of 201 cases was identified (mostly consults), including lymphoid hyperplasia of any morphology and cases with cysts in the setting of connective tissue disease (excluding culture positive, aspiration, and focal findings). Histologic patterns were reviewed and categorized as expansile lymphoid infiltrates (DELI), follicular bronchiolitis (FB), multinodular lymphoid hyperplasia (MNLH)

Results:

- Pathologic LIP was associated with autoimmune disorders, immunodeficiency or amiodarone. There were no idiopathic cases. Etiologies were not distinguished by the pattern of infiltrates.
- DELI, FB and MNLH were often seen in combination.
- Radiologic LIP was associated with autoimmune disorders in all cases.
- Poor overlap between pathologic and radiologic LIP cases
- MALT lymphoma was associated with 3-20% of cases in each morphologic subcategory; neoplastic areas in some cases had morphology indistinguishable from reactive areas.
- A paucity of plasma cells, the presence of non-necrotizing granulomas and OP were more common in immune deficiency than autoimmune disease, supporting overlap of

GLILD and LIP (though many immune deficiency cases didn't show dense lymphoid infiltrates)

Conclusions:

- "These data raise concerns about the practical use of the term LIP as currently defined…[LIP] does not present with sufficiently distinct findings to delineate such cases from other patterns of diffuse benign lymphoid proliferations…we believe LIP should be abandoned as a pathologic and radiologic diagnosis."
- Consider instead describing the findings as combinations of DELI, FB or MNLH
- Have a low threshold for lymphoma workup.
- Limitations: limited history on consult cases, not all had full lymphoma workup

Major pathological response exhibited distinct significance for lung adenocarcinoma post different modalities of neoadjuvant therapy.
Xia L, Guo J, Zhang HE, et al. Histopathol 2023;82:691-703. *Discussed by Jackie Chan*

Background: Major Pathologic Response (MPR) in post-neoadjuvant NSCLC is defined as <10% of residual viable tumor cells (RVT) in the tumor bed and is proposed as a predictor of survival.

Aim: To assess the clinical significance of %RVT in neoadjuvant chemo- & targeted-therapies

Methods: Retrospective review of 152 lung adenocarcinoma patients treated with neoadjuvant therapy (67 EGFR-targeted therapy and 85 chemotherapy). Clinicopathological characteristics, neoadjuvant treatment response and survival status were reviewed. Histologic review conducted by two pathologists blinded to patient outcomes.

Results

- MPR was observed in 26 of all patients (17.2%).
- Figure 1 (All patients): MPR status correlates with significantly different OS (p=0.03) but not RFS (p=0.44). By maximally selected log-rank statistics, best %RVT cutoff is 70%, which results in significant differences in RFS (p=0.043) and OS (p<0.01) for all patients.
- Figure 2 (chemotherapy only): By maximally selected log-rank statistics, 60% was best %RVT cutoff for RFS, and 70% for OS. They result in significantly worse RFS (p=0.02) and OS (p<0.01) in high RVT patients.
- Figure 3 (targeted therapy only): By maximally selected log-rank statistics, 35% was best %RVT cutoff for RFS, and 70% for OS. But they result in no significant differences in RFS (p=0.11) and OS (p=0.35) between patients with high vs low RVT.
- Table 3: By univariate and multivariate analyses, amongst targeted-therapy patients, ypN stage and high-grade patterns were independent prognostic factors for RFS and OS.
- Figure 4: Nomogram built based on ypN stage and high-grade patterns to predict 2 year RFS probability. 73% confidence in prediction accuracy.

Discussion

- Results in line with previous studies showing a 60-65% RVT being effective in predicting survival in neoadjuvant-treated adenocarcinoma patients.
- Data reaffirms the prognostic value of high-grade patterns in NSCLC.
- Limitations: Selection bias; limited follow-up times (median ~20 months) & sample size

Take Home Message

- RVT % is of prognostic value in patients with neoadjuvant chemotherapy-treated adenocarcinoma, but the 10% MPR cutoff is controversial.
- In setting of neoadjuvant targeted therapy, the presence of high-grade patterns and ypN stages are likely more useful than MPR for predicting prognosis.

Defining Morphologic Features of Invasion in Pulmonary Nonmucinous Adenocarcinoma With Lepidic Growth: A Proposal by the International Association for the Study of Lung Cancer Pathology Committee

Thunnissen et al, JTO

Background: The task of distinguishing invasion from lepidic pattern is a lot more relevant now that this determines T-stage, but it is not as easy as it sounds. The IASLC pathology committee formed an invasion working group aiming to evaluate reproducibility of invasion measurement and establish criteria to distinguishing invasive from lepidic pattern nonmucinous ADCA.

Methods: Blinded review of 32 cases (one scanned slide each) by 22 pathologists, followed by review of a separate cohort of 28 cases by 27 pathologists for which 9 were known to have LN mets or recurrence. Cases were reviewed in a stepwise fashion, first with just H&E, followed by addition of elastic stain and CK7. At each step each pathologist had to score as invasive, non-invasive, or don't know, and measure total tumor and invasion using digital ruler. A subset of 10 pathologists were then unblinded to the data including outcome, and met to re-analyze using a Delphi procedure to move towards a "correct" answer. Once criteria were selected, a validation cohort of 43 images were presented to the 10 pathologists, including "gut reaction" of invasion and assessment of invasion using criteria: **altered alveolar architecture**, **extensive epithelial proliferation** (EEP, multilayered cells 2 or more layers with higher nuclear grade lining alveolar spaces), **desmoplasia**, interstitial growth, high nuclear grade, nuclear shape (cuboidal, columnar, or pleomorphic), visible transition to higher cytologic grade, and alveolar macrophages. Major criterion in bold were scored for a total of 0-3.

Results

•Agreement for measuring tumor size was good (mean CV 7%) while measuring invasion was not good (mean CV 54%), with frequent notable special differences in the areas and sizes of invasion designated, with associated differences in T stage (see figure 4).

•Alveolar collapse (iatrogenic, surgical, atelectasis) was noted to lead to lepidic pattern with folding and tufting, that especially in the presence of thickened septa could mimic papillary, acinar or micropapillary growth. Partially mitigated by fixation through airways.

•Features favoring invasion include obvious things (effacement of alveolar architecture, invasion of pleura, vessels, airways, desmoplasia) and also EEP.

•Features favoring lepidic growth included iatrogenic collapse, single layer of monotonous cells, long axis of alveoli arranged in parallel (parallel streaming), and abrupt transition to type 1 pneumocytes with alveoli also arranged in parallel.

•Uninformative features included angulated glands, mature fibrotic/fibroelastotic scar, and alveolar septal thickening.

•Cytomorphology can be helpful but is not definitive. There are also factors that can complicate interpretation (poor fixation, equivocal microscopic features, collapse, etc).

•After a diagnostic algorithm was established, agreement for invasion based on 43 images was 79% using "gut reaction" and improved to 84% using the criteria. They had to exclude one observer to get these results.

Discussion:

It is difficult to provide more objective criteria to assess invasion in order to increase agreement- but data indicates even pulmonary expert pathologists vary widely in assessment of invasion. This is an effort to provide more clear guidance/criteria for invasion. They talk a lot about EEP in the discussion, and suggest it might represent the invasive clone colonizing alveolar spaces and thus should be considered invasive.

Take home message: Boy this is a tough task- valiant effort to improve reproducibility and present more clear criteria for invasion.

Clinicopathologic Features and Frozen Diagnostic Pitfalls of Bronchiolar Adenoma/Ciliated Muconodular Papillary Tumors (BA/CMPTs)

Ding et al, AJSP

Background: BA/CMPT includes both classical proximal type CMPTs with papillary architecture, ciliated cells, and mucinous cells, as well as distal/non-classical BAs with predominance of type2 pneumocytes and club cells. This morphological spectrum is unified by a continuous basal cell layer that expresses p40/p63, but recognition is difficult on frozen section. Other morphological challenges have also been identified, including basal cell hyperplasia, discontinuity of basal cells, and squamous metaplasia.

Methods: They found an astounding number of BA/CMPT to retrospectively study- 208 cases over 3 years. Frozen section was performed in 150. IHC analysis included TTF1, napsin, p40, p63 and CK 5/6.

Results

- 62% of patients were female, age range 15-79 years. 10 patients had 2 BA/CMPTs (usually in the same lobe) and 188 had a single lesion. Tumor size was 0.2-2 cm (median 0.6 cm); only 23 tumors were > 1cm. There was a lower lobe predominance, and all were peripheral. About 60% were solid nodules with the others were semi-solid or GGOs. Most patients (134) had other lesions resected, usually ADCA, so actually most of their cases were completely incidental. About 30% were proximal type, rest were distal.

- 150 cases had frozen section; 32 were called malignant or favor malignant (21%). The remainder were called BA (1), favor BA (57, 38%, about half proximal and half distal), favor reactive/metaplastic (32, 21%), or neoplasm defer to permanents (28, 19%). Distal type was more likely to be misdiagnosed as malignant on frozen section, and basal cell hyperplasia was also more likely to be called malignant [cells look squamous but lack atypia (uniform size & shape, no keratin), and have columnar or cuboidal cells on top]. Malignant misdiagnoses included non-mucinous ADCA as well as less frequently IMA.

Discussion

Tips for BA/CMPT on frozen section: beware adenocarcinomas < 1 cm (90% of BA/CMPTs fit this criteria). Conversely, diagnose BA/CMPT with caution if lesion is >1 cm. They note that distal-type BA/CMPTs were often contiguous with an airway- which I think may suggest overlap in diagnosis with florid peribronchiolar metaplasia, especially if multiple lesions are present. BAs should not show pleural retraction.

Take Home Points: BA/CMPT is tricky on frozen section. While classical proximal type CMPTs probably have good reproducibility, I think some of the distal type lesions maybe classified by some pathologists as other things (peribronchiolar metaplasia, etc.)- especially if multiple. This study is limited by the lack of follow-up- with such huge numbers, it would be nice to know they all behaved as we would expect (benign).

Articles for Notation

The impact of impaired tissue fixation in resected non-small-cell lung cancer on protein deterioration and DNA degradation
Butter et al, Lung Cancer

Summary: Analysis of 25 routinely fixed NSCLC resection specimens (wide variety of histologic types), with macroscopic assessment of fixation adequacy (gray-white=fixed, red=not fixed). Areas of adequate and inadequate fixation (recognized by basement membrane detachment) were marked on H&E, and a panel of IHC (ALK, PD-L1, Cam 5.2, CK7, c-MET, keratin MNF116, Napsin, p40, ROS1 and TTF1) were H-scored in well fixed and inadequately fixed areas, as well as in areas of necrosis. DNA was also isolated and measured for DNA fragmentation. All IHC showed a trend towards higher H-scores in adequately fixed areas, which was statistically significant for p40 and keratin MNF116. All stains showed geographic heterogeneity in staining intensity, regardless of fixation. DNA was fragmentation was an issue in all areas regardless of fixation adequacy, with fragments shorter than 300 bp regardless of fixation, but longer fragments (300-400 bp) were more concentrated in tumors with shorter fixation delay (< 6 hours) and short fixation time (< 24 hours).

Take home point: Poor fixation happens even using standard protocols, and is often admixed with adequately fixed areas in full sections from resections. Inadequate fixation can lead to weaker IHC staining, so focus on better fixed areas when interpreting stains. DNA degradation seems inevitable, but is reduced by fixing quickly (cold ischemic time < 6 hours) but not fixing for too long (< 24 hours).

Interstitial lung disease progression after genomic usual interstitial pneumonia testing
Chaudhary et al, ERJ

Summary: The described genomic classifier for UIP specifically predicts histologic UIP pattern, but whether it predicts outcome is unknown. This is a retrospective analysis of 192 interstitial lung disease patients who underwent bronchoscopy with genomic classifier testing and follow-up from 7 centers. 104 had a positive classifier, and 88 were negative. On multivariable analysis, a positive test showed a trend toward worse PFS (HR 1.58) but this was not significant (p=0.14); likewise, they showed a trend toward more rapid decline in FVC (difference -29 mL), but this was not significant (p=0.3).

Take home point: It seems patients selected for genomic classifier testing have a high rate of progressive ILD regardless of test result- therefore the test may have diagnostic value but not proven prognostic value.

Tobacco Smoking-Related Mutational Signatures in Classifying Smoking-Associated and Nonsmoking-Associated NSCLC
Ernst et al, JTO

Summary: Interesting study looking at genomic smoking signature instead of patient provided smoking history to divide 316 NSCLC into smoking related (smoking high) tumors and non-smoking related (smoking low) tumors. 169 tumors tested as smoking high, and 147 were smoking low. While this correlated with smoking history, 26% of patients with smoking history had smoking low tumors, and 4% of patient without smoking history had smoking high tumors. Interestingly, a few SQCCs were in the smoking low cluster. Smoking high tumors had a higher proportion of men, higher rate of non-ADCA histology, 5-fold higher TMB and mutational landscape, increased *KRAS* mutations, decreased *ALK/EGFR* mutations, and other differences in additional mutational signatures.

Take home point: Sometimes smokers get lung cancers that do not seem genetically related to smoking. Less commonly patients self-reporting as never smokers get lung cancers with a genetic smoking signature.

Frozen sections accurately predict the IASLC proposed grading system and prognosis in patients with invasive lung adenocarcinomas.
Fan et al, Lung Cancer

Summary: Chinese study of 373 stage I lung cancers that were retrospectively reviewed to determine tumor grade (IASLC grading system) by 3 pathologists including frozen section and final H&E slides. A prospective multicenter cohort of 212 stage IA cases were also analyzed. Interestingly, their surgeons did more aggressive surgery based on frozen section grading in 36 cases (wedge or segmentectomy converted to lobectomy). Overall concordance between frozen grade and final grade was 79% (kappa 0.65) in the retrospective cohort and 90% (kappa 0.729) in the prospective cohort. Complex glands/cribriform growth was an independent predictor of discordance (OR 2.193). It was slightly more common for them to overgrade on frozen section than undergrade. The interobserver agreement was 0.672 for the retrospective cohort and 0.752 for the prospective cohort. Both frozen section and final grade were significantly predictive of overall and recurrence free survival, with slightly better performance of final grade.

Take home point: They did a pretty good job of grading based on frozen section, except for properly classifying complex glands. Not sure if anyone would actually ask us to do this to determine intraop management- but their surgeons did. Their interobserver agreement data looks quite good also, which is a nice thing about having only 3 categories 😊.

Diagnostic efficacy of cryobiopsy for peripheral pulmonary lesions: A propensity score analysis
Furuse et al, Lung Cancer

Summary: Retrospective comparison of 492 cryobiopsies performed for peripheral lesions to 2,232 sampled by conventional transbronchial biopsy methods (forceps or needle aspiration), including a matched analysis. In the matched analysis, cryobx had higher diagnostic yield (89% vs. 78%, OR=2.36, p<0.001); a positive diagnosis was considered either a definitive diagnosis of malignancy, or a specific benign diagnosis that fit with the clinical and radiographic follow-up. They noted that cryobiopsy was particularly efficacious compared to standard methods for lesions in the RML/lingula or bilateral lower lobes, non-solid lesions/GGOs, and lesions that were not visible on CXR. Interestingly, cryobx was not superior for upper lobe lesions and lesions visible on CXR. The higher diagnostic yield came with a higher rate of significant bleeding (38% vs. 10%), but no life threatening bleeding episodes were observed. One patient that underwent cryobx suffered a stroke after the procedure.

Take home point: Cryobx works for peripheral lesions, and has higher diagnostic yield especially for GGOs, lesions not visible on CXR, and those in middle/lower lung zones. Cryobx does have a higher rate of significant bleeding, but no life-threatening bleeding was observed.

Expression of paired box 9 defines an aggressive subset of lung adenocarcinoma preferentially occurring in smokers
Hayashi et al, Histopathology

Summary: They analyzed 71 lung adenocarcinoma samples using transcriptome sequencing, and identified that PAX9 expression strongly and inversely correlated with expression of TTF-1. They then analyzed 1083 invasive lung adenocarcinomas for TTF-1 and PAX9 by IHC. PAX9 was expressed in normal ciliated airway epithelial cells and basal cells, and in 28% of lung adenocarcinomas, although only 4% were diffuse and strong. 88% of PAX9 positive tumors co-expressed TTF-1, so the expression patterns did not necessarily lead to decreased protein expression patterns. PAX9 positive tumors were significantly associated with heavy smoking, non-lepidic growth patterns (especially acinar), EGFR wild-type and high PD-L1 expression; interestingly, all these were oppositive associations compared to the TTF-1 positive/PAX9 negative group. PAX9 was associated with decreased overall survival (p=0.02).

Take home point: Interesting marker that seems to identify an aggressive subset of lung adenocarcinoma.

TTF-1 Expression and Clinical Outcomes of Combined Chemoimmunotherapy in Patients With Advanced Lung Adenocarcinoma: A Prospective Observational Study

Katayama et al, JTO CCR

Summary: Multicenter prospective cohort of 58 patients with advanced lung ADCA with known pre-treatment TTF1 status by IHC. Objective response rate to chemoimmuno therapy was higher in TTF1-positive group (p=0.02), with associated longer PFS and OS. TTF1 expression was an independent predictor of favorable prognosis on multivariable analysis, and was associated with higher PD-L1 expression.

Take home point: Not sure if clinical teams would ever be interested in knowing TTF1-status as a prognostic factor for chemoimmuno response, but expression is favorable.

Progressive Disease With Low Survival in Adult Patients With Pulmonary Fibrosis Carrying Surfactant-Related Gene Mutations-An Observational Study
Klay et al, Chest

Summary: Retrospective study of the clinical course of 23 Dutch patients with pulmonary fibrosis and underlying surfactant gene mutations (ABCA3, SFTPC, SFTPA2), compared to a cohort of 248 patients with other familial pulmonary fibrosis and 575 with IPF. Patients with surfactant gene mutations often presented at younger age, were more often female, and presented with worse PFTs (lower FVC, lower DC). Rate of decline and transplant-free survival (44 months) were similar to the other 2 groups. A few patients were treated with antifibrotics with stabilization of lung function, while those treated with immune modulation had variable response.

Take home point: Patients with pulmonary fibrosis secondary to surfactant protein mutations have poor outcome with progressive fibrotic lung disease, and may have some benefit from antifibrotics.

Nationwide differences in cytology fixation and processing methods and their impact on interlaboratory variation in PD-L1 positivity
Koomen et al, Virchows Arch.

Summary: Dutch study of the effects on cytology fixative and cell block prep procedures on PD-L1 results. Cytology processing data gathered via questionnaire and correlated with PD-L1 results from a national registry (1458 PD-L1 results from cytology material performed at participating labs) . 28 participating labs (66% response rate) reported 19 different combinations of fixative and cell block prep methods, highlighting the variability in this process. Fixation methods included formalin, alcohol, CytoLyt, and CytoRich Red. Cell block methods included centrifugation and FFPE, agar-based cell block, Thermo Scientific method, and Cellient cell block. PD-L1 positivity rates significantly varied based on patient sex, histologic subtype,

fixative used, as well as cell block preparation method. Positivity rate was highest for samples fixed in formalin; positivity rates were up to 20% lower using other methods when a 1% PD-L1 cutoff was considered, and up to 10% lower at the 50% PD-L1 cut off. When considering cell block methods, agar-based cell blocks gave higher PLD1 positivity rates, and Cellient seemed lower compared to FFPE. 8 labs showed significant difference in the mean PD-L1 positivity rate to the national average, which reduced to 5 when controlling for fixative and cell block prep method.

Take home point: Fixative and cell block prep are widely variable, and lead to predictable differences in PD-L1 positivity rates.

Conventional and radiomic features to predict pathology in the preoperative assessment of anterior mediastinal masses
Mayoral et al, Lung Cancer

Summary: Retrospective radiographic CT analysis of 239 benign mediastinal masses and 180 with malignant thymic tumors (59% thymoma, 10% thymic carcinoma, plus various others) who underwent thymectomy. 25 "conventional" visually based characteristics were analyzed, and 101 radiomic features were extracted by a computer and used for machine learning analysis. A model to predict malignancy combining visual and radiomic features worked best compared to each individually (AUC 0.715); similarly, a combined model worked best to predict thymic carcinoma vs. thymoma (AUC 0.81).

Take home point: This CT-based computer model did a good job of differentiation thymic carcinoma vs. thymoma using CT features, and a moderate job of differentiating benign from malignant lesions. Might be helpful in pre-op planning.

Quantifying the Value of Multigene Testing in Resected Early Stage Lung Adenocarcinoma
Muthusamy et al, JTO

Summary: They looked at their comprehensive genetic profiling data in 6697 patients in an effort to try and discern any benefits to testing tumors before advanced disease (i.e. reflex testing on all early stage tumors). About one-third of their patients had genetic testing before they developed advanced disease/diagnosis. No surprisingly, they found that patients were able to be treated faster at the time of discovery of recurrent if testing had already been done (median 3.6 weeks vs. 6 weeks, $p<0.001$). They also found that immune checkpoint inhibitor therapy could have been avoided in some patients with *ALK, ROS1* or *RET* drivers, at a savings of $1597 per patient relative to *EGFR* testing alone.

Take home point: Reflexive comprehensive genetic profiling of early stage lung adenocarcinomas leads to faster treatment at the time of recurrence, and avoids immune

checkpoint inhibitor therapy in the small subset of patients with *ALK, ROS1* or *RET* drivers, which may offset some of the cost.

Liquid biopsy-based decision support algorithms for diagnosis and subtyping of lung cancer
Visser et al, Lung Cancer

Summary: Blood of 683 patients with suspected lung cancer was prospectively subjected to a liquid biopsy panel including 8 protein tumor markers and analysis for circulating tumor DNA containing *EGFR, KRAS* and *BRAF* mutations. About 80% of patients actually had lung cancer. (90% NSCLC, 10% small cell) They analyzed the performance of the tumor markers to predict small cell vs. non-small cell lung cancer. They found combinations of tumor markers and circulating tumor DNA mutations that could detect lung cancer at 65% sensitivity, NSCLC at 67% sensitivity, and small cell at 50% sensitivity.

Take home point: They got informative information from liquid biopsy in about two-thirds of patients with suspected lung cancer- they particularly advocate this method may be helpful in patients with non-diagnostic biopsies or tumors that are hard to reach.