

**Journal Club**  
**Henry D. Tazelaar, M.D.**  
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**Articles for Discussion**

**1. Weiss ST. Biological network modeling and systems biology to advance our understanding of lung disease. Am J Respir Crit Care Med. 2016;194(8):920-21.**

Although the next article by Kusko, et al is the article up for consideration, I found this editorial of Weiss helpful in putting this study into a broader context. The work is important because of its use of a novel way of looking at human disease in the context of systems biology and biological network modeling.

As an example, Weiss indicates that the principles used in the Kusko article are related to graphical models used to explain how a variety of seemingly disparate data types (the neural network of the worm *Caenorhabditis elegans*, the power grid of the United States, and collaboration between actors) could all be explained by a simple type of network called the scale-free network. The characteristics of these networks are that they have many peripheral nodes (connecting points) and a few highly connected nodes (hubs). These networks have a few universal organizing principles including a “small-world” property (i.e., they are highly connected with relatively short paths between nodes), are robust to failure, such that peripheral nodes can be knocked out and network function preserved, and node number can be described by a power law function (think proportionally related factors). All biological data (biochemical, transcriptional, epigenomic, protein-protein interactions) can be accurately modeled using scale-free networks. Systems biology is a holistic approach to numerous forms of data including such things as genomics, proteomics, etc. that can also be applied to the level of the cell, organ, organism or population taking a snapshot of the varying data types and applying network analysis. Within this context others have postulated that there is a human disease network in which common genes connect diseases to each other, and that clustering of diseases in the human disease network/interactome is a result of genes that are shared, or unshared between clustering diseases. In this context the article by Kusko, et al begins to make sense.

**2. Kusko RL, Brothers II JF, Tedrow J, Pandit K, Huleihel L, Perdomo C, Liu G, Juan-Guardela B, Kass D, Zhang S, Lenburg M, Martinez F, Quackenbush J, Scirba F, Limper A, Geraci M, Yang I, Schwartz DA, Beane J, Spira A, Kaminski N. Integrated genomics reveals convergent transcriptomic networks underlying chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2016;194(8):948-60.**

At the outset let me say that I have no idea exactly what the authors did. I only understood parts of this article but thought that with the editorial it made a fairly fascinating read at a superficial level.

**Background:** Despite shared environmental exposures to cigarette smoke, IPF and COPD are usually studied in isolation and the presence of shared molecular mechanisms is unknown. This study set out to mine for abnormal gene fusions and cytogenetic abnormalities in the lung and blood of patients with COPD and IPF.

**Methods:** The authors describe the transcriptional repertoire of patients with COPD, IPF compared to normal controls using a host of molecular techniques. Tissue was obtained from the Lung Tissue Research Consortium (LTRC).

Study was comprised of patients with COPD with predominant emphysema, 19; COPD without predominant emphysema, 17; IPF, 19; COPD with indeterminant phenotype, 13; and normal, 20. Pathologists categorized the tissue (about the only part of the study I understood).

The following techniques were used: RNA extraction, mRNA-Seq, mRNA and miRNA microarray processing, gene filtering, differential expression using the limma package, comparison of mRNA arrays with mRNA-seq, immunohistochemistry, integration of miRNA and mRNA data, and the ultimate identification of alternative splicing events.

**Results:** In brief, the authors identified that the p53/hypoxia pathway is common to both disorders with over expression of several genes in its pathway, notably hypoxia-inducible factor-1 alpha, mouse double minute-2 homolog, and nuclear factor kappa B inhibitor  $\beta$  are over expressed in both diseases relative to normal lung samples.

Importantly genes that distinguished IPF or emphysema from normal controls were changed in concordant directions but not always with changes of the same magnitude.

A brief scan of the figures in the article might give you an idea of the complexity of the data and undoubtedly the elegance of this study. Figure 5 gives you a sense for the systems thinking that goes into the interpretation of this data.

**Discussion:** This study purports to be the most in depth profile of the core lung transcriptome in health and disease using NSG.

Despite extremely divergent phenotypes, IPF and emphysema share the same environmental risk factor and the unexpected and novel findings of the study may shed significant light on the potential core pathways that initiate chronic lung remodeling in response to environmental injury.

Limitations of the study include overall small numbers and inability to distinguish gene expression changes that are causal versus a consequence of the disease, and that some of the control lungs were collected from smokers with adjacent lung cancer.

**Comment:** Fascinating stuff and I am glad there are people out there who understand it!

### **3. Kawabata Y, Shimizu Y, Hoshi E, Ikeya T, Kurashima K, Takayanagi N. Acute ischaemic lung injury due to pulmonary vascular obstruction. *Histopathology*. 2016;69:647-54.**

**Background:** The main causes of pulmonary infarction include PTE and pulmonary tumors with secondary obstruction. Obstruction classically causes reversible hemorrhage or irreversible infarction. The authors encountered a previously undescribed distinctive lobule-sized myxomatous or fibrous alveolar wall thickening around infarctions and speculated that this may have been due to ischemia or obstruction. The study was initiated to study this observation further.

**Methods:** Review of 2142 lobectomy bi-lobectomy and pneumonectomy cases, 720 SLBs and 79 autopsies for pulmonary infarctions and acute ischemic lung injury (AILI). Definition of the latter is “focal alveolar wall thickening (myxomatous, fibrous, or a mixture), with epithelial metaplasia, and negligible inflammation, the size of which is up to one lobule”. Was more often seen in proximity to an infarct and the nearby alveoli being almost normal as opposed to the usual type of acute lung injury which shows diffuse involvement and luminal exudation with subsequent organization? After review of all of the samples, the study group comprised 69 cases (60 from lobectomies, 7 from SLB, 2 from autopsy). Confirmation of histology was made by two pathologists. Cases were stained with VVG and IHC (AE1/AE3, CD34, collagen type 4, vimentin, T cells, and B cells) and results semi-quantitatively graded.

**Results:**

- AILI lesions were identified in 34 patients with infarction (approximately 50%).
- AILI lesions were located around infarctions.
- Alveolar wall thickness varied with 24% of cases showing moderate thickness.
- Diffuse cuboidal cell metaplasia with occasionally atypical changes were observed in 34 cases.
- AILI was more common in men and in younger patients.

**IHC results:**

- Partial disruption of epithelial continuity noted in 48% of cases
- Separation of alveolar epithelial and capillary BMs observed to varying degrees in 75% of cases
- Centralization of the capillaries detected in 71% of cases
- Increase in number of vimentin-positive spindle cells was noted in all cases

**Discussion:** Authors conclude that the histologic features of AILI are characterized by “noninflammatory, myxomatous or fibrous thickening of alveolar wall with frequent BM separation and an increase in the number of vimentin-positive spindle cells”. The reason for male dominance in younger age in the infarction group is unclear.

AILI was observed almost exclusively in the infarction group suggesting that severe local ischemia due to vascular obstruction is a necessary precursor.

Early stage AILI is characterized by myxomatous swelling indicating that fibroblasts may become activated and synthesize and secrete a precursor of hyaluronic acid following alveolar wall injury.

The authors present a suspected sequence of acute ischemic changes ( see Figure 4).

AILI is distinct from “partial infarction” as described by Corrin and Nicholson (characterized by “capillary destruction, pulmonary hemorrhage, acute inflammation and preserved basic architecture”).

**Comment:** It is a bit unclear to me why we need another term to describe what really looks like interstitial organization of acute lung injury (Ala, Katzenstein and Myers).

4. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J, International Society for Heart and Lung Transplantation. **The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report – 2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. 2016;35(10):1170-84.**

**Background:** Each year the ISHLT presents registry data for all patients undergoing lung transplantation.

Highlights include:

- Most common indications include COPD without A1ATD, IIP, COPD with A1ATD, ILD, not IIP, CF and retransplant
- Most transplants performed are now bilateral/double lung (as opposed to a single lung)
- Median survival for all comers is now 5.8 years and is best for patients with cystic fibrosis and worst for those who undergo retransplantation or who have other IIPs

Major causes of mortality within first 30 days include graft failure and non-CMV infections with other significant contributors being multiorgan failure, cardiovascular and technical causes. After the post-transplant year OB/BOS, graft failure and CMV cause the most deaths. Malignancy also becomes an important contributor to mortality.

Risk factors significantly associated with mortality in the first post-transplant year include male gender, type of underlying disease, pretransplant steroid use, retransplantation, earlier era of transplant, increased severity of illness at the time of transplantation, donor causes of death, higher rate of HLA and CMV mismatch.

Based on follow-up from July 2004 to June 2015, 28% of adult lung transplant surviving recipients had at least one episode of treated rejection between discharge and one year of follow-up.

BOS, conditional on survival to two weeks remains a common long-term complication with 76% developing BOS by ten years post-transplant.

**Conclusions:** Number of lung transplants has increased while heart/lungs have decreased.

Survival for both types has improved over time mainly due to survival in the early post-transplant.

**Comment:** Not much new here but for those who don't follow this I thought it was worth a quick review.

**5. Ichinose J, Shinozaki-Ushiku A, Nagayama K, Nitadori J, Anraku M, Fukayama M, Nakajima J, Takai D. Immunohistochemical pattern analysis of squamous cell carcinoma: lung primary and metastatic tumors of head and neck. Lung Cancer. 2016;100:96-101.**

**Background:** A common problem in surgical pathology is distinguishing a primary lung cancer from a solitary metastasis of squamous carcinoma in patients with a history of head and neck squamous cell carcinoma (HNSCC). These authors aim to develop a new diagnostic algorithm for primary LSCC and pulmonary metastases from HNSCC on the basis of IHC.

**Methods:** Useful antibodies were identified by extracting the top 50 genes which were markedly and differently expressed between LSCC and HNSCC comparing expression profiles between 10 LSCCs and 18 HNSCCs using the Affymetrix U133A GeneChips. They then selected the top three antibodies for which IHC was available including CK19, matrix metalloprotein H3 (MMP3) and antibodies to peptidase inhibitor 3 (PI3). IHC staining was evaluated by four grades according to percent of positive tumor cells: 95%, 50-95%, 5-50%, and less than 5%.

Tissue microarrays from FFPE including 39 LSCCs, from patients without HNSCC and 48 HNSCCs at the primary site were used as the training set. Staining was defined as negative when less than 5%. From this they developed their algorithm and a validation was performed using 32 LSCCs from patients without a history of HSNCC and 23 HNSCCs at the primary site. The specimens analyzed in the training set were excluded from the validation set.

The algorithm was then applied to 28 patients with a history of HNSCC who underwent resection of pulmonary squamous tumors between 1999 and 2014. All tumor sections of indeterminate pulmonary tumors and original tumors were analyzed according to the algorithm. They then defined retrospective diagnoses as follows:

- Tumors that recurred after pulmonary resection were diagnosed as metastases of HNSCC whereas tumors without recurrence were diagnosed as LSCC
- Recurrence-free probability (RFP) was calculated from the date of surgery until documentation of disease recurrence.
- In cases without recurrence any death due to causes other than LSCC and HNSCC were censored.
- Statistical analyses were performed using appropriate software and diagnostic ability was evaluated by calculating sensitivity, specificity, and accuracy.

**Results:** LSCCs had a tendency for being CK19 positive and, MMP3 and PI3 negative. Figure 3 below shows the diagnostic algorithm. Utilizing this algorithm the diagnostic utility for HNSCC was

- Sensitivity – 96%; specificity – 44%; accuracy – 65%
- Positive predictive value 65%
- Negative predictive value 93%
- The IHC diagnosis coincided with the retrospective diagnosis in 22 (79%) of 28 patients (sensitivity, 95%; specificity, 44%)

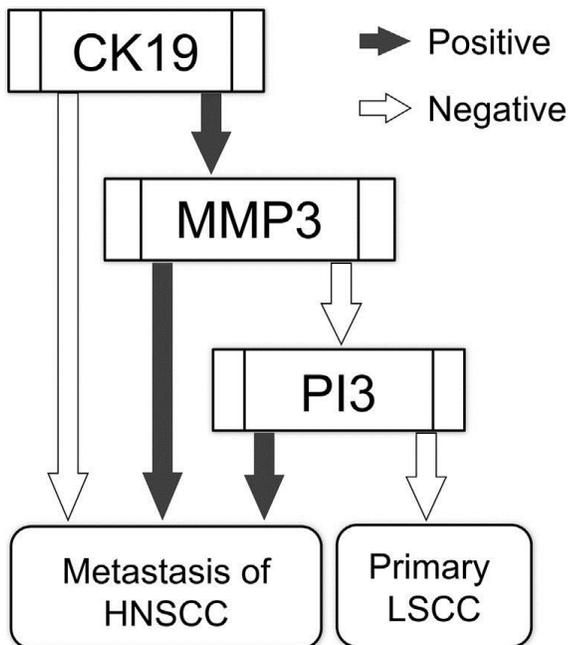


Fig. 3.

The schema of the IHC diagnostic algorithm. The black arrows represent positive staining, whereas the white arrows stand for negative staining. LSCC, lung squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma.

IHC diagnosis of indeterminate tumors also clearly predicted the risk of tumor recurrence (more likely in patient with HNSCC).

Other interesting observations had to do with more routine histologic feature including the fact that lung cancers tended to be more moderate to poorly differentiated while primary HNSCCs tended to be better differentiated. P16 proved not useful.

**Discussion:** In this study the authors were able to establish an IHC diagnostic algorithm which contained satisfactory accuracy in both the training and validation sets. The IHC diagnosis of indeterminate tumors could also clearly predict for tumor recurrence.

Limitations: there may well be tumor heterogeneity and some differences in staining were noted.

This study used primary HNSCCs and not known metastases. Ultimate diagnosis was based on likelihood of recurrence and pattern of recurrence which tended to favor HNSCCs.

Number relatively small, single institution, etc

**Comment:** Interesting approach with readily available antibodies. Might be worth a confirmatory study.

## Neoplastic I Lung

1. Zakowski MF, Rekhtman N, Auger M, Booth CN, Crothers B, Ghofrani M, Khalbuss W, Laucirica R, Moriarty AT, Tabatabai AL, Barkan GA. Morphologic accuracy in differentiating primary lung adenocarcinoma from squamous cell carcinoma in cytology specimens. *Arch Pathol Lab Med.* 2016;140:1116-20.

**Background/Objective:** To evaluate accuracy and interobserver variability among cytopathologists in subtyping NSCLC using cytologic preparations. Seventy percent (70%) of lung cancers are diagnosed on limited material such as FNA, transbronchial or thoracic needle specimens.

**Methods:** Nine cytopathologists from different institutions submitted cases of NSCLC with surgical followup.

Cases independently blinded and reviewed by each cytopathologist and a diagnosis of adenocarcinoma, or squamous carcinoma was rendered on stained slides.

A major disagreement was defined as a case being misclassified three or more times.

Cytopathologists were asked to classify as ADC or SqCC and the state of diagnosis was made by morphology alone or IHC was needed to determine the subtype.

No attempt was made to apply IASLC/ATS/ERS classification.

**Results:** Total n=93 cases (69 ADC, 24 SqCC).

- Of 818 chances (93 x 9 pathologists), 753 correct diagnoses were made (92% overall accuracy).
- 25/69 cases of ADC (36%) and 7 of 24 cases of squamous carcinoma (29%) had a disagreement ( $p=.16$ ).
- Touch preps were more frequently misdiagnosed compared with other specimens.
- Diagnostic accuracy of each cytopathologist varied from 78.4% to 98.7% (mean 91.7%).
- IHC was helpful or necessary in 81 of 376 cases (21%).
- In some cases where IHC was available, pathologists indicated it was not needed or useful in making their diagnosis.
- In cases where IHC was not available (442) there were 53 miscalculations for an error rate of 12%. There were five errors in 376 cases where IHC was available but not used in diagnosis (13% error rate).
- Lowest error rate (0%) was in those cases where IHC was available and used to classify the tumors.
- Kappa for morphology only cases was  $\kappa = 0.617$  compared to cases with IHC ( $\kappa = .464$ ). The authors suggest that the slightly lower kappa value may be attributed to cases where IHC was available but not used for diagnosis.

**Conclusions:** Lung ADC can be accurately distinguished from SqCC by morphology in cytologic specimens with excellent interobserver concordance.

**Comment:** I guess I liked this quote the best: “certain types of cytology specimens were associated with greater error rates, specifically cytology TPs of core biopsies. In fact, the use of TPs from core biopsies of lung specimens can result in the deletion of cellularity and DNA content of the cores”. Amen. Who started this practice???

**2. Hashimoto H, Kurata A, Fujiwara M, Hara K, Matsumoto J, Kusakabe M, Tachibana K, Nashiro T, Terado Y, Akahane M, Usui K, Suzuki Y, Kondo H, Kama H, Kuroda M, Horiuchi H. Solitary pulmonary capillary hemangioma of adult cases: clinicopathologic characteristics as an unrecognized entity. Am J Surg Pathol. 2016;40:1380-89.**

**Background:** The authors describe an unusual vascular lesion which resembles pulmonary capillary hemangiomatosis.

**Methods:** All cases were identified in the database of the NTT Medical Center and Kyorin University Hospital. All were Asian patients diagnosed over a seven year period.

Authors performed clinical radiologic and histologic and immunohistochemical review.

**Results:** Seven original cases were treated with surgery, median age 54 (range 19-58) with four women and three men. All patients were asymptomatic and nodules were detected by CT scan. Nodules were partially solid with one being pure ground glass.

Size ranged from 5 to 20 mms. SPCH manifested as a solitary lesion composed of densely proliferating and dilated capillaries without cytologic atypia, growing within alveolar septa. The lesions also were identified to spread into vascular lumens and involved the walls of bronchioles and protrusion into bronchiolar lumens.

IHC: uniformly expressed endothelial markers including CD31, CD34, factor VIIIr antigen; alpha smooth muscle actin positive cells were also observed.

These lesions are quite subtle histologically and they are well photographed in the article.

All patients had benign follow-up.

**Conclusions:** Heightened awareness of this unusual lesion may lead to further knowledge about its true epidemiology and prevalence.

**Comment:** If I have ever seen one of these, I have misdiagnosed it!

**3. Pokharel S, Dhillon SS, Ylang L, George S, Yendamuri S. Sclerosing pneumocytoma with lymph node metastasis. J Thorac Oncol. 2016;11(10):1802-4.**

A case report of a 33-year-old woman with a 2.5 cm sclerosing pneumocytoma who was found to have metastatic tumor in one peribronchial lymph node.

**Comment:** Nothing new here but nicely illustrated.

4. **Naito M, Aokage K, Saruwatari K, Hisakane K, Miyoshi T, Hishida T, Yoshida J, Masato S, Kojima M, Kuwata T, Fujii S, Ochiai A, Sto Y, Tsuboi M, Ishii G. Microenvironmental changes in the progression from adenocarcinoma in situ to minimally invasive adenocarcinoma and invasive lepidic predominant adenocarcinoma of the lung. Lung Cancer. 2016;100:53-62.**

**Background/Objective:** The aim of this study was to investigate microenvironmental changes during the development of adenocarcinomas from AIS through MIA to LPA.

**Methods:** AIS n = 51, MIA n=59, LPA-S (small) less than 3 cms, n=113 and LPA-L (large) greater than than 3 cms, n=47.

Cases were evaluated for expression levels of epithelial-mesenchymal transition-(EMT) related molecules (E-cadherin, S100A4), invasion-related molecules (laminin-5 and ezrin), stem cell-related molecules (ALDH-1) and growth factor-related markers (podoplanin) Cancer -associated fibroblast (PDPN+ CAFs), CD204-positive tumor associated macrophages (CD204+ TAMs,) and CD34+ endothelial cells were also analyzed.

**Results:** No significant differences were found between LPA-S (small) and LPA-L (large). Laminin-5 expression in noninvasive carcinoma component of MIA was significantly higher than that of AIS ( $p < 0.001$ ).

During progression from NIA to LPA-S, the expression of laminin-5 in invasive carcinoma component was significantly elevated ( $p < 0.01$ ).

Tumor promoting stromal cells were more frequently recruited into the invasive area of LPA-S. Ezrin expression in the invasive component of LPA-L was significantly increased ( $P < 0.05$ ) compared to LPA-S; the number of tumor promoting stromal cells were not different between the two groups.

**Conclusion:** These results suggest to the authors that microenvironmental molecular changes occur during the progression from MIA to LPA-S and also suggest that this process may play an important role in disease progression from AIS to LPA.

5. **Jiang GY, Zhang XP, Zhang Y, Xu HT, Wang L, Li QC, Wang EH. Coiled-coil domain-containing protein 8 inhibits the invasiveness and migration of non-small cell lung cancer cells. Human Pathology. 2016;56:64-73.**

**Background:** Previous studies have implicated coiled-coil domain-containing protein 8 (CCDC8) as a tumor suppressor in several types of cancer. CCDC8 proteins are involved in such things as regulation of gene expression, cell division and membrane fusion.

**Methods:** Primary specimens from 147 patients with NSCLC who underwent complete resection comprised study group: 70 SqCC and 77 ADC

Histologic grade and clinicopathologic features were correlated with IHC for CCDC8. Additional molecular testing was performed including in A549 cell line with CCD8, determining their ability to invade and migrate using a number of more sophisticated techniques.

**Results:** Among 147 cases only 37.4% (55/147) had detectable CCDC8 expression; however, 70% (21/30) of adjacent normal lung tissue showed positive CCDC8 expression.

- Several features were significantly associated with CCD8 including tumor differentiation ( $p=0.39$ ), as well as TNM stage ( $p=0.009$ ) and the presence of lymph node metastases ( $p=0.038$ ).
- Kaplan-Meier showed that CCDC8 expression level affected overall survival with those expressing CCDC8 living significantly longer than those without (45.7 versus 39.1 months,  $p=0.043$ ). CCDC8 was not found to be an independent prognostic factor.
- Additional studies showed that CCDC8 inhibits lung cancer cell invasion and migration.

**Discussion:** CCDC8 may suppress invasion and metastases of lung cancer cells and may represent promising therapeutic target for NSCLC.

**6. Goto A, Dobashi Y, Tsubochi H, Maeda D, Ooi A. MicroRNAs associated with increased AKT gene number in human lung carcinoma. Human Pathology. 2016;56:1-10.**

I started to read this article, and about 1/3 through realized it was WAY above my head. So, please feel free to access the article and dig in if this is your thing. ☺

**7. Cheng TYD, Cramb SM, Baade PD, Youlten DR, Nwogu C, Reid ME. The International Epidemiology of Lung Cancer: latest trends, disparities, and tumor characteristics. J Thorac Oncol. 2016;11(10):1653-71.**

**Introduction:** Aim was to update global lung cancer epidemiology and describe changing trends and disparities.

**Methods:** Data on lung cancer incidence and mortality were extracted from GLOBOCAN 2012, an International Agency for Research on Cancer (IARC) project, providing contemporary national estimates of cancer statistics for 184 countries.

Countries were classified into four levels of development (very high, high, medium, or low) according to the 2012 HDI composite index developed by the U.N. Development Program.

**Results:**

- Incidence was highest in countries with very high HDI and lowest in countries with low HDI
- In most countries with very high HDI, the incidence in males decreased, incidence in females continued to increase
- Histologic types varied but adenocarcinoma was more common than squamous particularly among women
- Five year survival rate varied from 2% (Libya) to 30% (Japan) with substantial within country differences

There is a lot more in this article but those are the broad, general trends. There is also a section on molecular profile. Numerous graphs by country are also present.

**Conclusion:** A global disease burden of lung cancer is likely to increase well through the first half of this century given global trends in incidence and mortality, and the small improvements in survival.

Any primary prevention will necessarily include stronger tobacco control initiatives at the government level in addition to coordinated efforts to improve the air and environmental quality.

**Comment:** A great resource for general lung cancer discussions particularly if you are traveling!

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### **Circulating DNA/Liquid Biopsy Articles**

Although not strictly speaking anatomic pathology related, we at least need to be familiar with the world of diagnostic molecular testing for patients with lung cancer. The latest technique is “liquid biopsy”. The next series of articles are all related and I highlight them for your perusal. The editorial by Wang (see below) sums up the current literature thus “after nearly a decade of exploration and development, detection of EGFR activating and resistance mutations on the basis of plasma ctDNA has gradually been applied in clinical practice of NSCLC, finally becoming the prerequisite and basis for accomplishing precision management of lung cancer. Urinary DNA and CTC based genetic detection (CTC = circulating tumor cell) based genetic detections will enrich the utility of liquid biopsy after undergoing large sample multi-center studies.”

8. **Wang S, Wang J. Are liquid biopsies ready for prime time of clinical applications? J Thorac Oncol. 2016;11(10):1606-8.**
9. **Crosbie PAJ, Shah R, Krysiak P, Zhou C, Morris K, Tugwood J, Booton R, Blackhall F, Dive C. Circulating tumor cells detected in the tumor-draining pulmonary vein are associated with disease recurrence after surgical resection of NSCLC. J Thorac Oncol. 2016;11(10):1793-97.**
10. **Reck M, Hagiwara K, Han B, Tjulandin S, Grohé C, Yokoi T, Morabito A, Novello S, Arriola E, Molinier O, McCormack R, Ratcliffe M, Normanno N. ctDNA determination of EGFR mutation status in European and Japanese patients with advanced NSCLC: The ASSESS Study. J Thorac Oncol. 2016;11(10):1682-89.**
11. **Reckamp KL, Melnikova VO, Karlovich C, Sequist LV, Camidge DR, Wakelee H, Perol M, Oxnard GR, Kosco K, Croucher P, Samuels E, Vibat CR, Guerrero S, Geis J, Berz D, Mann E, Matheny S, Rolfe L, Raponi M, Erlander MG, Gadgeel S. A highly sensitive and quantitative test platform for detection of NSCLC EGFR mutations in urine and plasma. J Thorac Oncol. 2016;11(10):1690-700.**
12. **Jiang T, Zhai C, Su C, Ren S, Zhou C. The diagnostic value of circulating cell free DNA quantification in non-small cell lung cancer: a systematic review with meta-analysis. Lung Cancer. 2016;100:63-70.**
13. **Suda K, Murakami I, Yu H, Ellison K, Shimoji M, Genova C, Rivard CJ, Mitsudomi T, Hirsch FR. Heterogeneity of EGFR aberrations and correlation with histologic structures: analyses of**

**therapy-naïve isogenic lung cancer lesions with EGFR mutation. J Thorac Oncol. 2016;11(10):1711-17.**

Interesting case report based on an autopsy from an 81-year-old non-smoking woman with lung adenocarcinoma who could not receive any systemic therapy because of her poor performance status.

**Methods:** After her death, 15 tumor specimens from different sites were obtained. Expression of mutant EGFR protein and EGFR gene copy numbers were assessed by IHC and ISH. Heterogeneity of these EGFR aberrations was compared between metastatic sites and histologic structures (micropapillary versus non-micropapillary).

**Results:** All lesions showed positive staining for mutant EGFR protein except for 40% of the papillary component in one of the pulmonary metastases.

Expression of mutant specific EGFR protein was significantly higher in micropapillary components than non-micropapillary components ( $p=0.014$ ).

EGFR gene copy number was quite different between lesions but did not correlate with histologic structure.

EGFR gene copy numbers were similar between histologic structures in each lesion.

**Conclusion:** These data indicate that expression of EGFR mutant protein and copy number do not change as a consequence of tumor progression.

- This justifies using biopsy specimens from metastases as a surrogate for primary tumors.
- Useful case report which helps to answer some of the longstanding questions regarding EGFR testing.

**14. Vannucci F, Gonzalez-Rivas D. Is VATS lobectomy standard of care for operable non-small cell lung cancer? Lung Cancer. 2016;100:114-19.**

**Background:** Review article describing the history of VATS lobectomy for operable NSCLC.

Sections discussed include:

1. Introduction – historical note and brief summary of VATS evolution
2. VATS versus open thoracotomy – lymph node dissection and oncological efficacy
3. VATS versus open thoracotomy for lung cancer – extended resections beyond lobectomy
4. VATS versus open thoracotomy – crucial postoperative outcomes: complications, pain, quality of life and survival
5. VATS lobectomy for lung cancer – indications and contraindications
6. Discussion and conclusion

**Conclusion:** Authors conclude VATS lobectomy is feasible, safe, cost effective and an oncologically appropriate procedure especially in the hands of a skilled surgeon and team.

**15. Walsh K, Kheng YC, Oniscu A, Harrison DJ, Wallace WA. Could molecular pathology testing in lung cancer be more cost-effective? J Clin Pathol. 2016;69:938-41**

**Background:** EGFR and ALK are routinely studied in patients with NSCLC but limited resources require molecular pathology services to be cost effective without harming patients.

**Methods:** Audit of molecular pathology testing in Southeast Scotland Cancer Network.

**Results:** TTF1 IHC had high negative predictive value for EGFR mutations (99%). Reflex testing of all NSCLC had the highest cost.

Limiting testing to those who might be considered for treatment, however, would lead to a cost reduction of only 7.5%.

Serial testing, however, could save 32.7%.

**Conclusions:** Testing only patients being considered for EGFR and ALK inhibitors represent a small savings.

More significant savings would be achievable if testing algorithms using known associations between clinical markers were developed.

**Comment:** Interesting article with a few surprising results.

## Neoplastic Pleura

1. **Churg A, Attanoos R, Borczuk AC, Chirieac LR, Galateau-Sallé F, Gibbs A, Henderson D, Roggli V, Rusch V, Judge MJ, Srigley JR. Dataset for reporting of malignant mesothelioma of the pleura or peritoneum: recommendations from the International Collaboration on Cancer Reporting (ICCR). Arch Pathol Lab Med. 2016;140:1104-10.**

New recommendations from ICCR on the dataset for reporting mesotheliomas – somewhat similar to CAP cancer protocols. Of note, mitotic count is listed as one of the data elements even though the authors admit it has not been definitively established as an independent parameter in the diagnostic setting or as a determinant of prognosis.

2. **Hida T, Hamasaki M, Matsumoto S, Sato A, Tsujimura T, Kawahara K, Iwasaki A, Okamoto T, Oda Y, Honda H, Nabeshima K. BAP1 immunohistochemistry of *p16* FISH results in combination provide higher confidence in malignant pleural mesothelioma diagnosis: ROC analysis of the two tests. Pathol Int. 2016;66:563-70.**

**Background:** Another article on BAP1 IHC and p16 FISH.

**Methods:** BAP1 IHC and p16 specific FISH was performed on 40 malignant pleural mesotheliomas and 20 reactive mesothelial hyperplasia cases.

Diagnostic accuracy for MPM and cut-off values for the two methods were assessed using receiving operator characteristic (ROC) analysis.

### Results:

- BAP1 expression loss, present in 68%.
- p16 homozygous deletion (HD) present in 67.5%
- Both loss of BAP-1 and p16 deletion – 42.5%.
- All 20 RMH cases had neither BAP1 loss nor p16 HD.
- Combination showed higher sensitivity (92.5%) and estimated probability than BAP1 IHC or p16 specific FISH alone.

**Conclusions:** BAP1 IHC and p16 specific FISH have independent prognostic value an increase for liability when used in combination for MPM diagnosis.

**Comment:** Similar to other papers which have been produced that using both markers is more sensitive for the diagnosis of MPM.

3. **Hylebos M, Van Camp G, van Meerbeeck JP, de Beeck KO. The genetic landscape of malignant pleural mesothelioma: results from massively parallel sequencing. J Thorac Oncol. 2016;11(10):1615-26.**

This is a review describing alterations that have identified in the genetic pathways of the development of malignant mesothelioma including:

- The tumor protein p53/DNA repair

- Cell cycle
- Mitogen-activated protein kinase
- Phosphoinositide 3-kinase (PI3K/AKT pathways)

**Conclusions:** As these pathways are important during tumor development, they provide interesting candidates for novel drug targets.

**Comment:** Nice summary of a lot of background work being done in this area.

## Non-neoplastic Lung

1. Eddens T, Campfield BT, Serody K, Manni ML, Horne W, Elsegeiny W, McHugh KJ, Pociask D, Chen K, Zheng M, Alcorn JF, Wenzel S, Kolls JK. A novel CD4<sup>+</sup> T cell-dependent murine model of *pneumocystis*-driven asthma-like pathology. *Am J Respir Crit Care Med.* 2016;194(7):807-20.

**Objective:** The authors sought to explore the role of PCP in generating asthma like lung pathology.

**Methods:** Pneumocystis infection or antigen treatment was used to induce asthma-like pathology in wild-type mice.

Presence of anti-pneumocystis antibodies in human serum samples was detected by ELISA and Western blotting.

### Results:

- Pneumocystis infection generated a strong type 2 response in the lung which requires CD4+ T-cells.
- Pneumocystis infection was capable of priming a Th2 response similar to that of commonly studied airway allergen, the house dust mite.
- Pneumocystis antigen treatment was capable to inducing allergic inflammation in the lung resulting in anti-pneumocystis IgE production, goblet cell hyperplasia and increased airway resistance.
- In humans, patients with severe asthma had increased levels of anti-pneumocystis IgG and IgE compared with healthy controls.

**Conclusions:** This study demonstrates for the first time that pneumocystis is an airway allergen capable of inducing asthma-like lung pathology.

2. Shah A, Armstrong-James D. Opportunist turns allergen: double life of *pneumocystis jirovecii* in asthma. *Am J Respir Crit Care Med.* 2016;194(7):779-93.

Editorial to accompany the pneumocystis study. Highlights some possible weaknesses in the current study but overall think that the authors have made an important observation.

3. Raouf S, Bondalapati P, Vydyula R, Ryu JH, Gupta N, Raouf S, Galvin J, Rosen MJ, Lynch D, Travis W, Mehta S, Lazzaro R, Naidich D. Cystic lung diseases: algorithmic approach. *Chest.* 2016;150(4):945-65.

Review article including radiology and pathology with nice algorithm diagram and imaging. Pathology limited to a few shots of PLCH, LAM, light chain deposition and cystic PCP.

**Comment:** Nice review for reference.

**4. Gomez DC, Medrad B. Eosinophilic pneumonia associated with pirfenidone therapy. Eur Respir J. 2016;48:1240-42.**

Letter to the editor/case report documenting pirfenidone, induced eosinophilic lung disease diagnosed by BAL eosinophilia at 22%. .

Authors comment that this may be underdiagnosed or underreported since it is indistinguishable from IPF exacerbation.

Highlights the importance of the differential of IPF exacerbations and emphasizes the importance of a thorough workup including BAL for respiratory deteriorations in patients with ILD.