

# The impact of the new 2015 WHO classification of lung cancer: Pathologist's view

Prof Keith M Kerr

Department of Pathology,

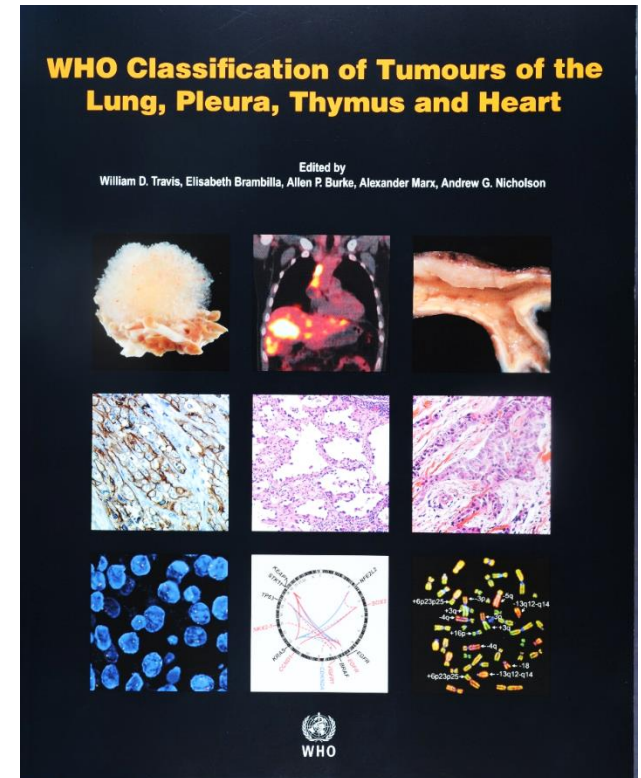
Aberdeen University School, Aberdeen Royal Infirmary, UK

# Disclosures

- I have acted as consultant for Roche Genentech, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, Clovis, Bristol Myers Squibb, Merck Sharp Dohme
- I have received honoraria for speaker bureau from Roche Genentech, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, Bristol Myers Squibb

# Background

- Reviewed approx. every 10 years
- Traditionally a classification for surgically resected lung cancers
- For pathologists.....
- Multidisciplinary team working.....and awareness
- Evolving therapy diversity
  - Need to do better with small samples
- Molecular data on lung cancer





# IASLC Pathology Committee



# WHO classification of lung cancer: what is it?

- A list
- A classification
- A biologically and clinically meaningful division of lung cancers according to their
  - Morphological features
  - Biological features
  - And their molecular features.....
- Practical and widely applicable

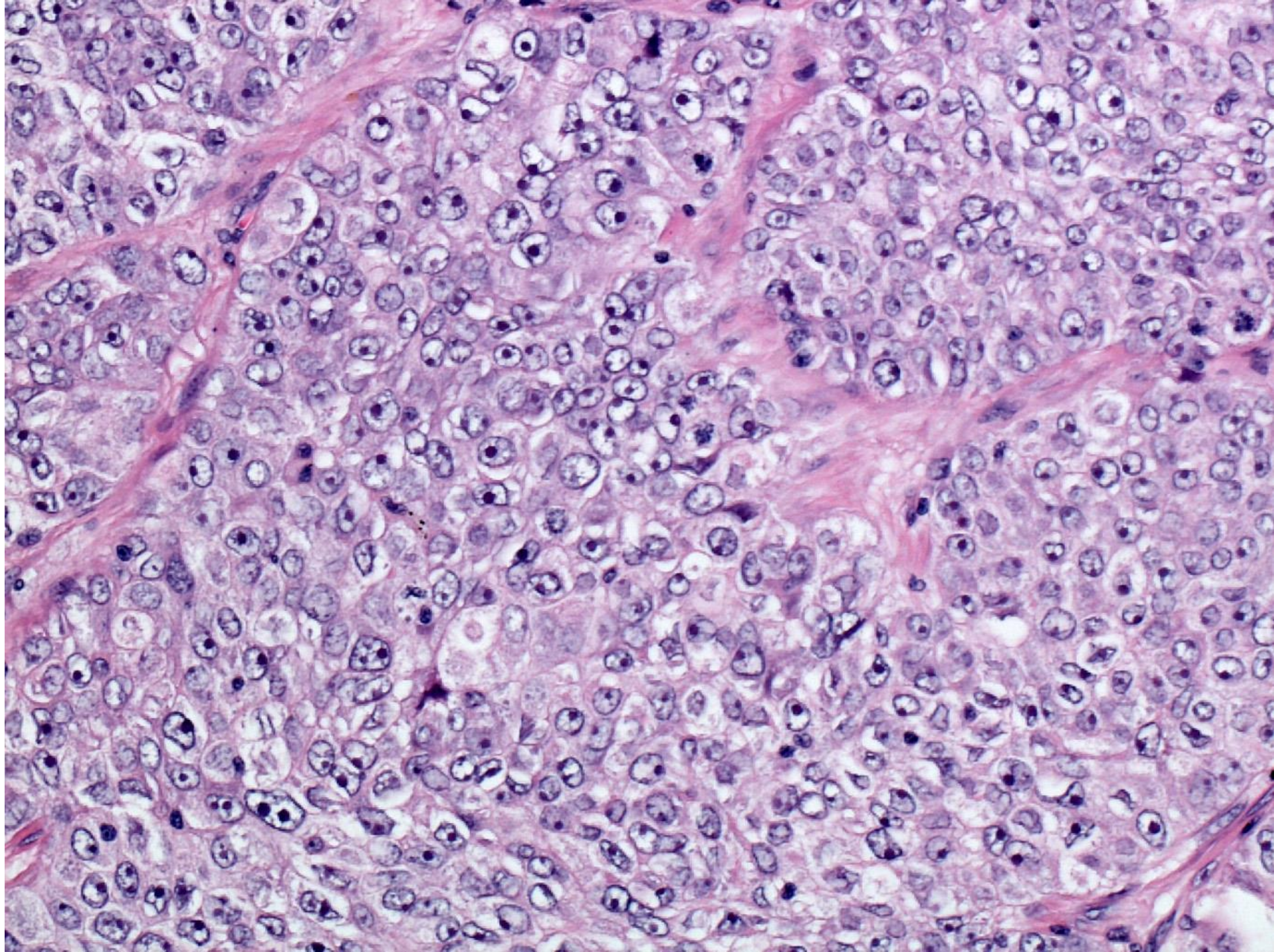
# What has changed?

- Definitions of Large cell carcinoma
- Several issues with adenocarcinoma
- Little change for squamous cell carcinoma
- New category of 'neuroendocrine tumours'
- Consolidate recommendations for small sample diagnosis

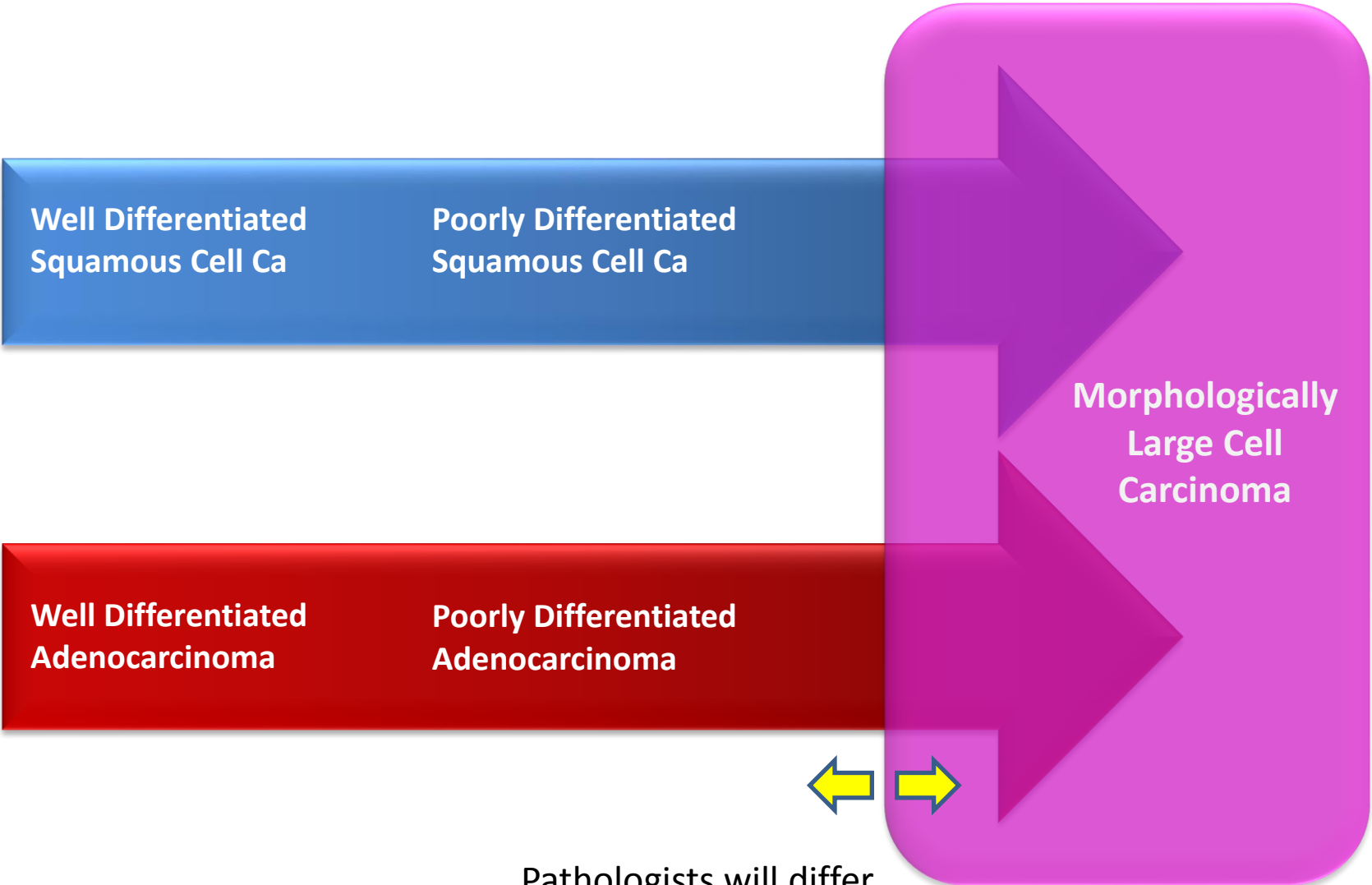
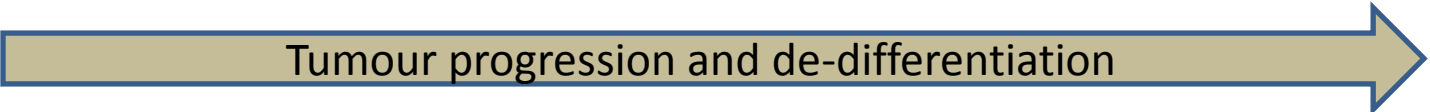


Large cell  
carcinoma

Largely  
a diagnosis  
of exclusion





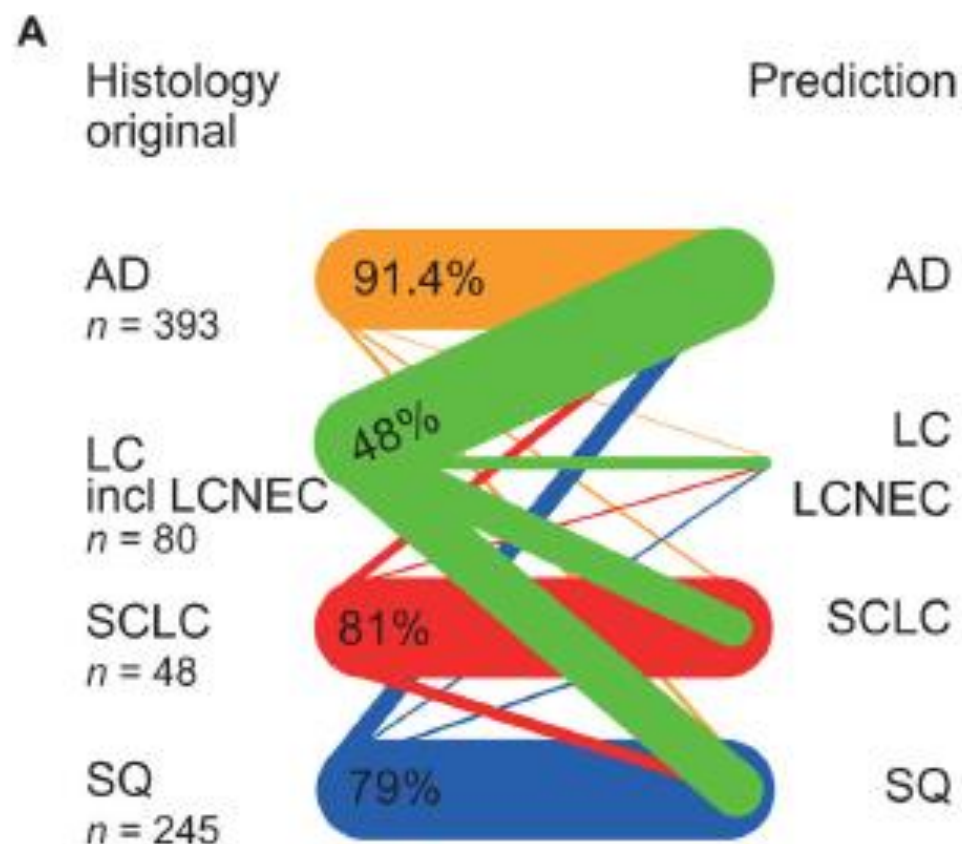
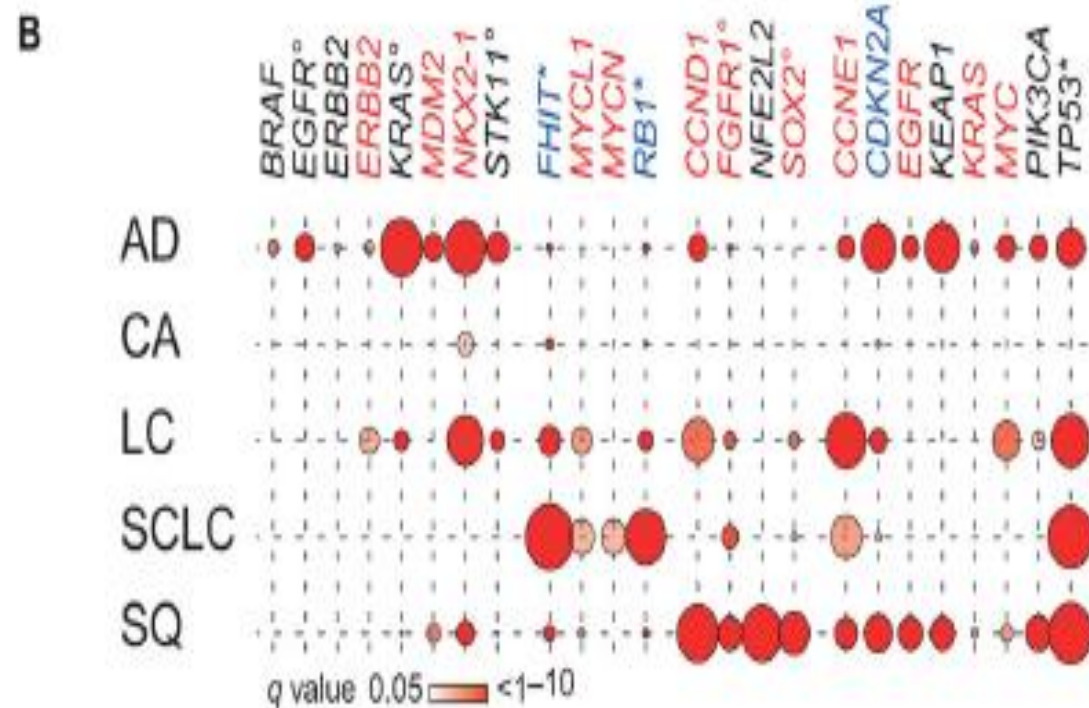


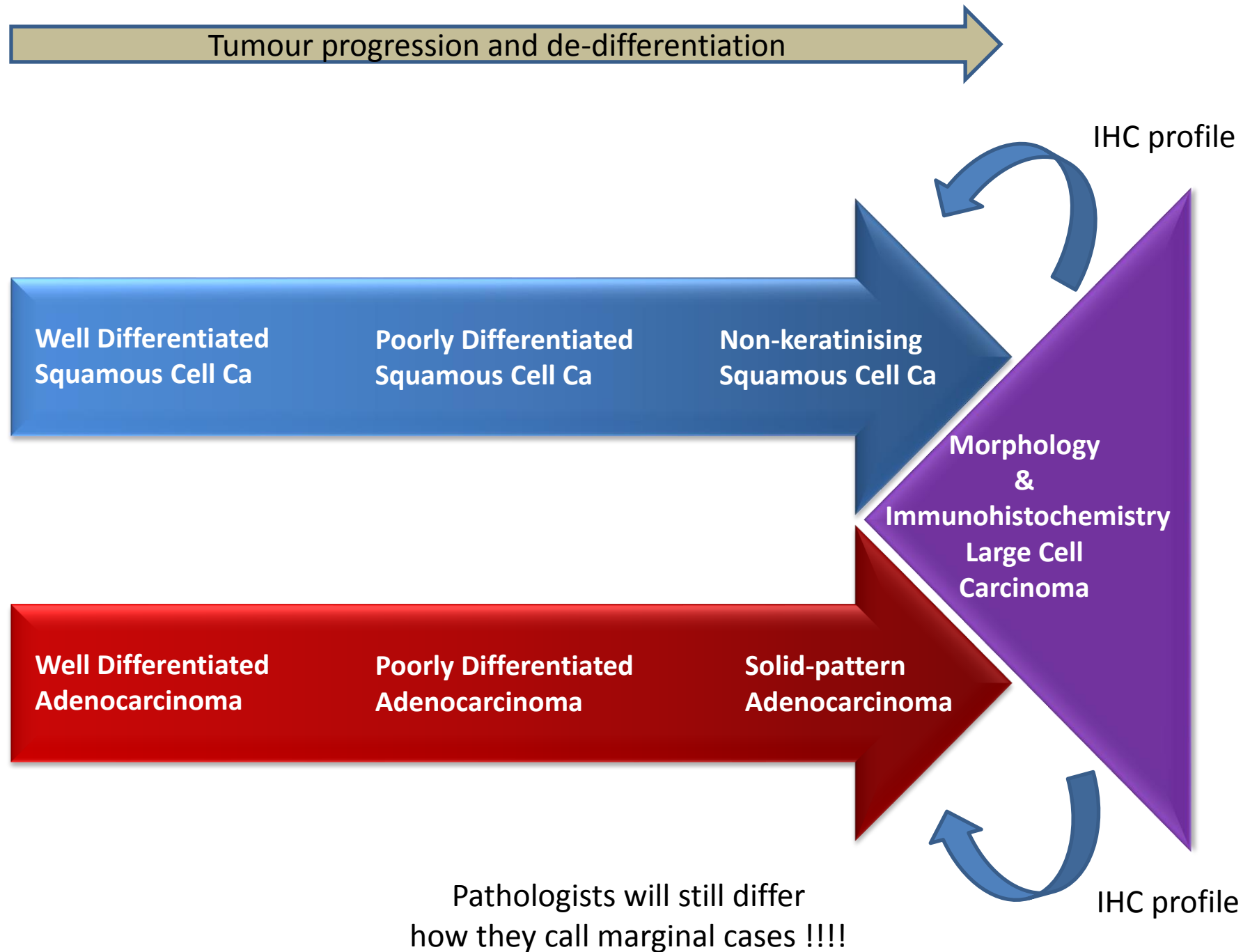


# A Genomics-Based Classification of Human Lung Tumors

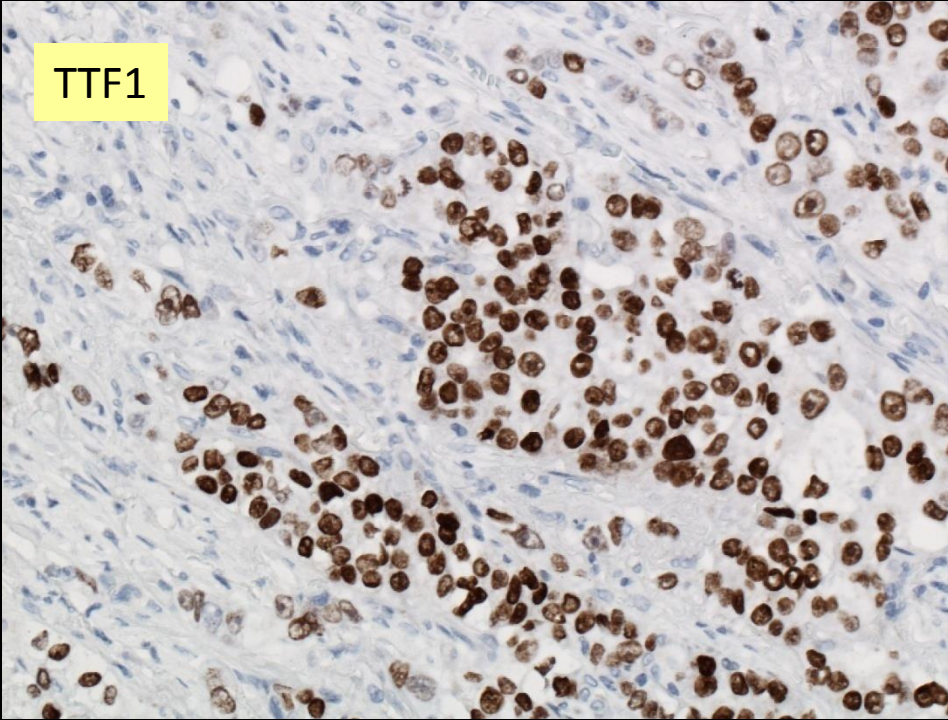
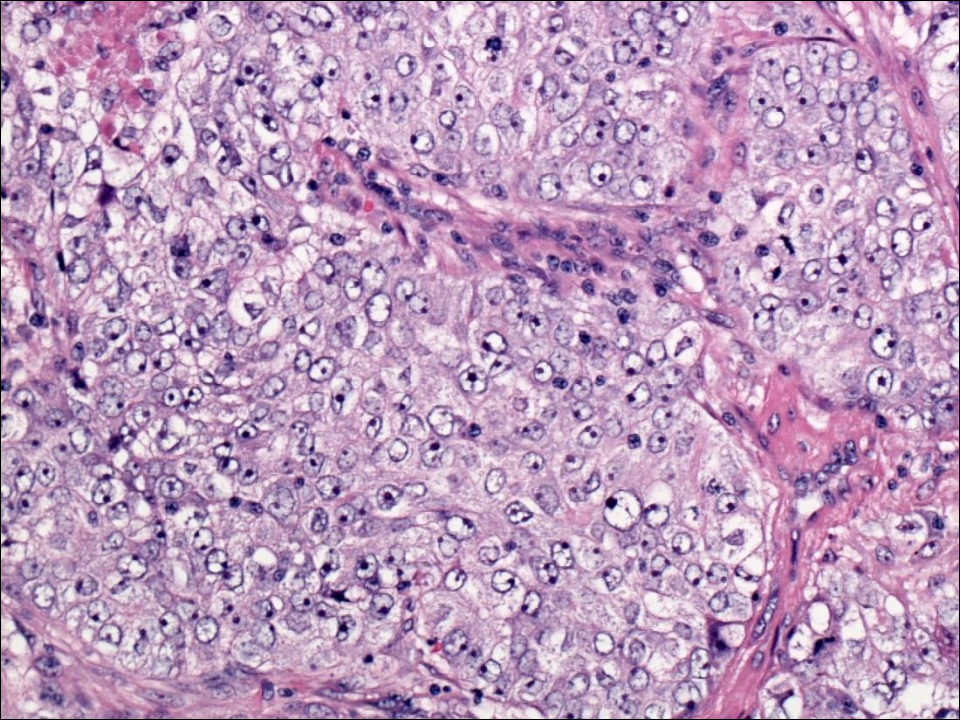
The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM)

*Sci Transl Med.* 2013 October 30; 5(209): 209ra153. doi:10.1126/scitranslmed.3006802.

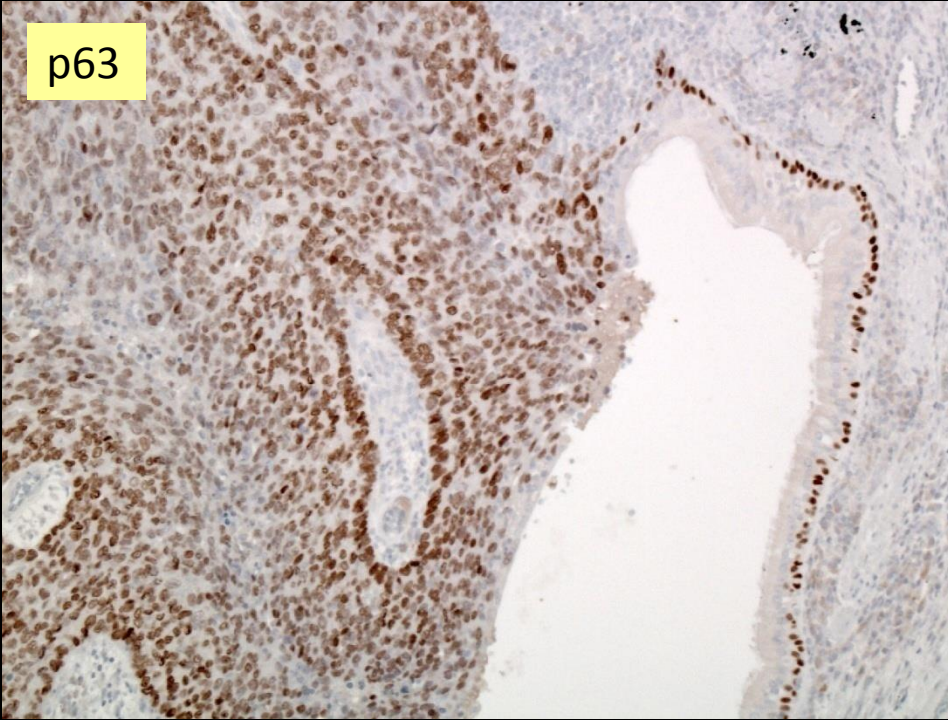
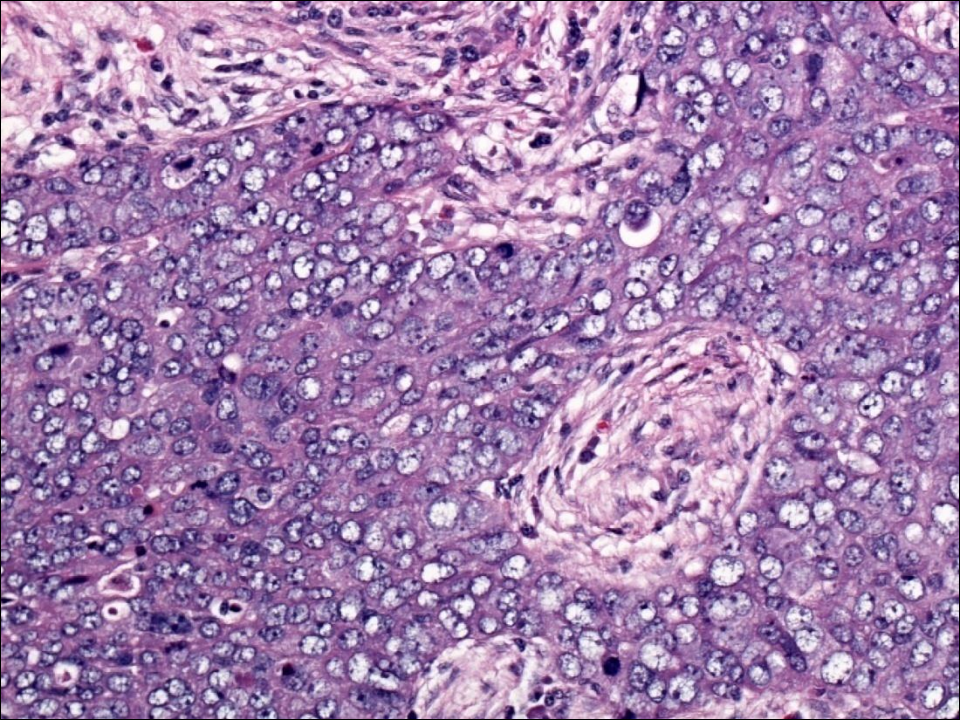








Adenocarcinoma:  
Solid subtype



Non-keratinizing  
Squamous cell  
carcinoma



# Diagnosis of Large Cell Carcinoma: 2015

## Definition

Large cell carcinoma is an undifferentiated non-small cell carcinoma (NSCC) that lacks the cytological, architectural, and **immunohistochemical features** of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma. The diagnosis requires a thoroughly sampled resected tumour, and cannot be made on non-resection or cytology specimens.

The diagnosis of large cell carcinoma is only made when additional staining (*Immunohistochemistry and/or mucin stains*) is **negative, unclear, or not available**.

# Clinical impact

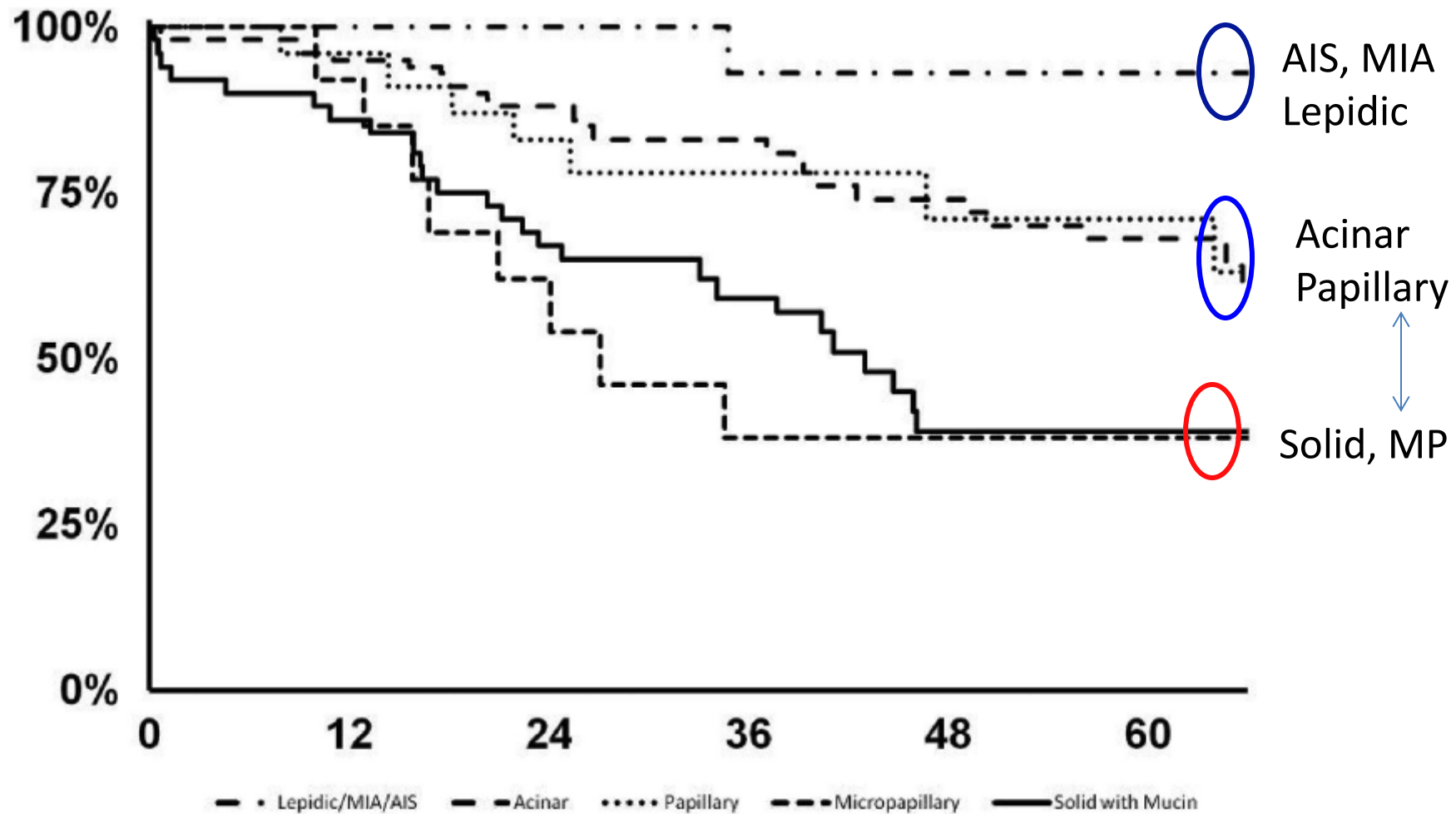
- Large cell category gets smaller
- Classification shift may reduce post-operative 5YS for squamous cell and adenocarcinomas
- No impact on molecular testing practice
- New nomenclature

# Adenocarcinoma: changes

- Bronchiolo-alveolar cell carcinoma is no more!
  - BAC becomes AIS (adenocarcinoma in situ)
- Minimally invasive adenocarcinoma (MIA)
- Surgically resected adenocarcinomas classified by predominant pattern



# Post operative survival vs **predominant pattern** in pulmonary adenocarcinoma – five patterns

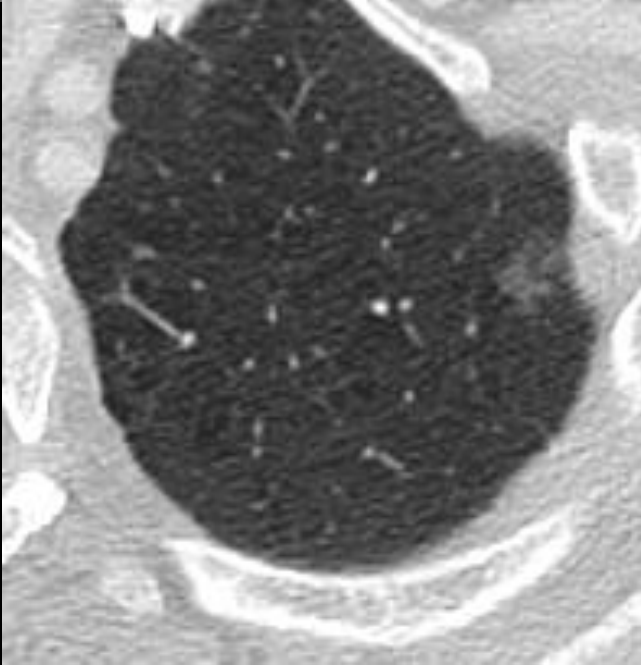
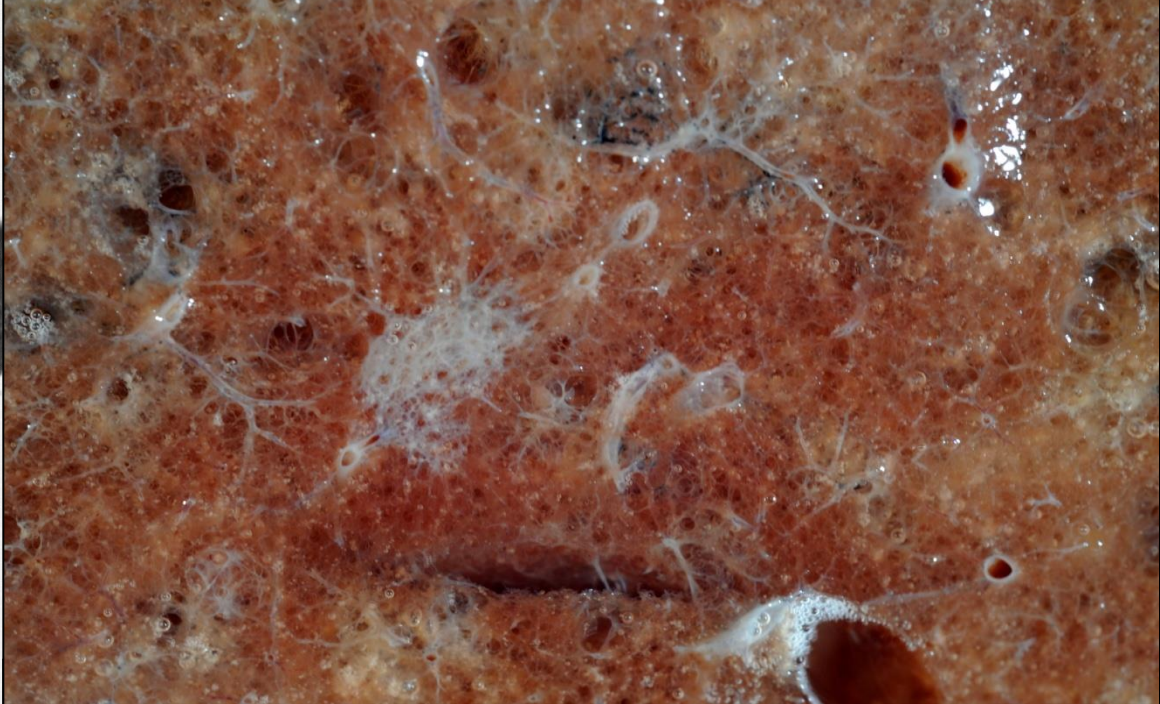


Yoshizawa A et al. Mod Pathol 2011; 24, 653-664  
Russell P et al. J Thorac Oncol 2011; epub June  
Warth A et al. J Clin Oncol 2012; Mar 5 epub

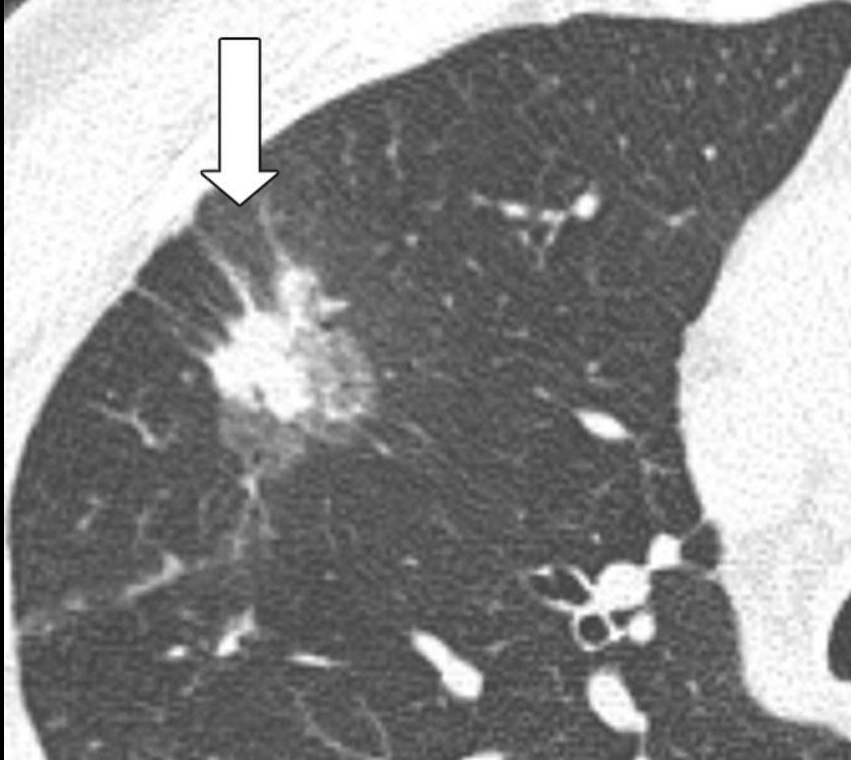
Stage 1 only  
Stages 1-3  
Stages 1-4

# Adenocarcinoma: changes

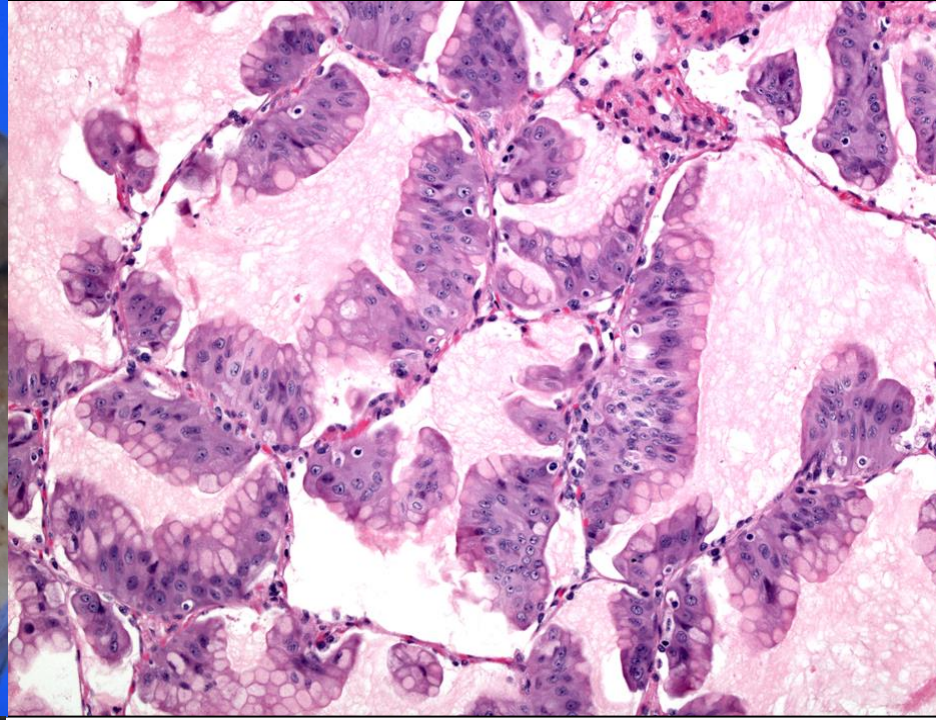
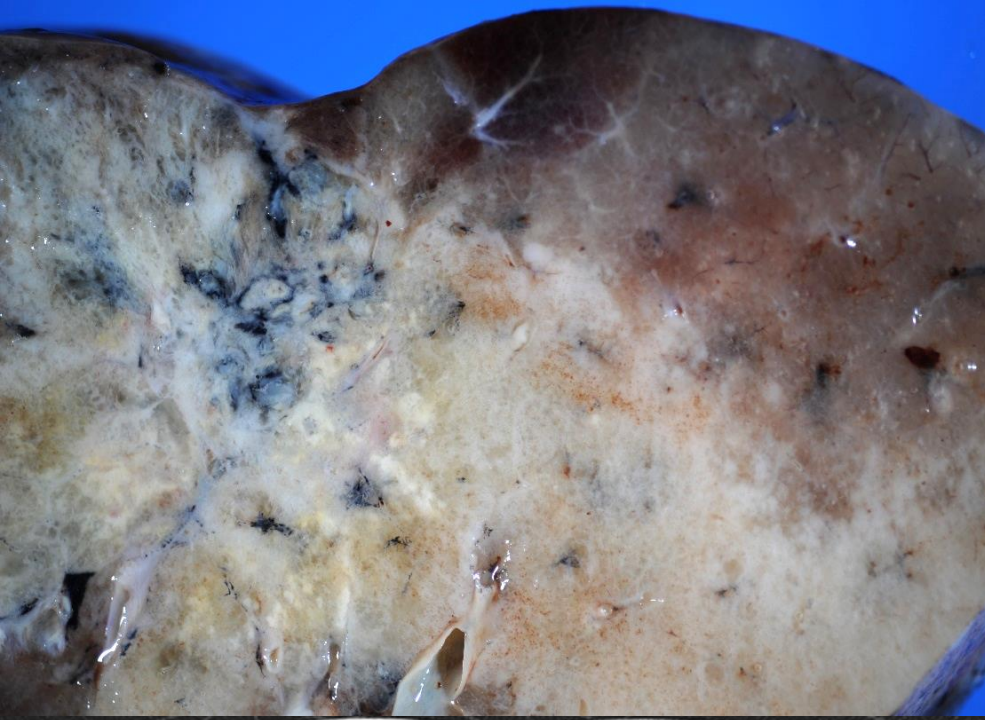
- Bronchiolo-alveolar cell carcinoma is no more!
  - BAC becomes AIS (adenocarcinoma in situ)
- Minimally invasive adenocarcinoma (MIA)
- Surgically resected adenocarcinomas classified by predominant pattern
- Promote better understanding of relationship between the lepidic pattern and ground glass change on CT
- Invasive mucinous adenocarcinoma









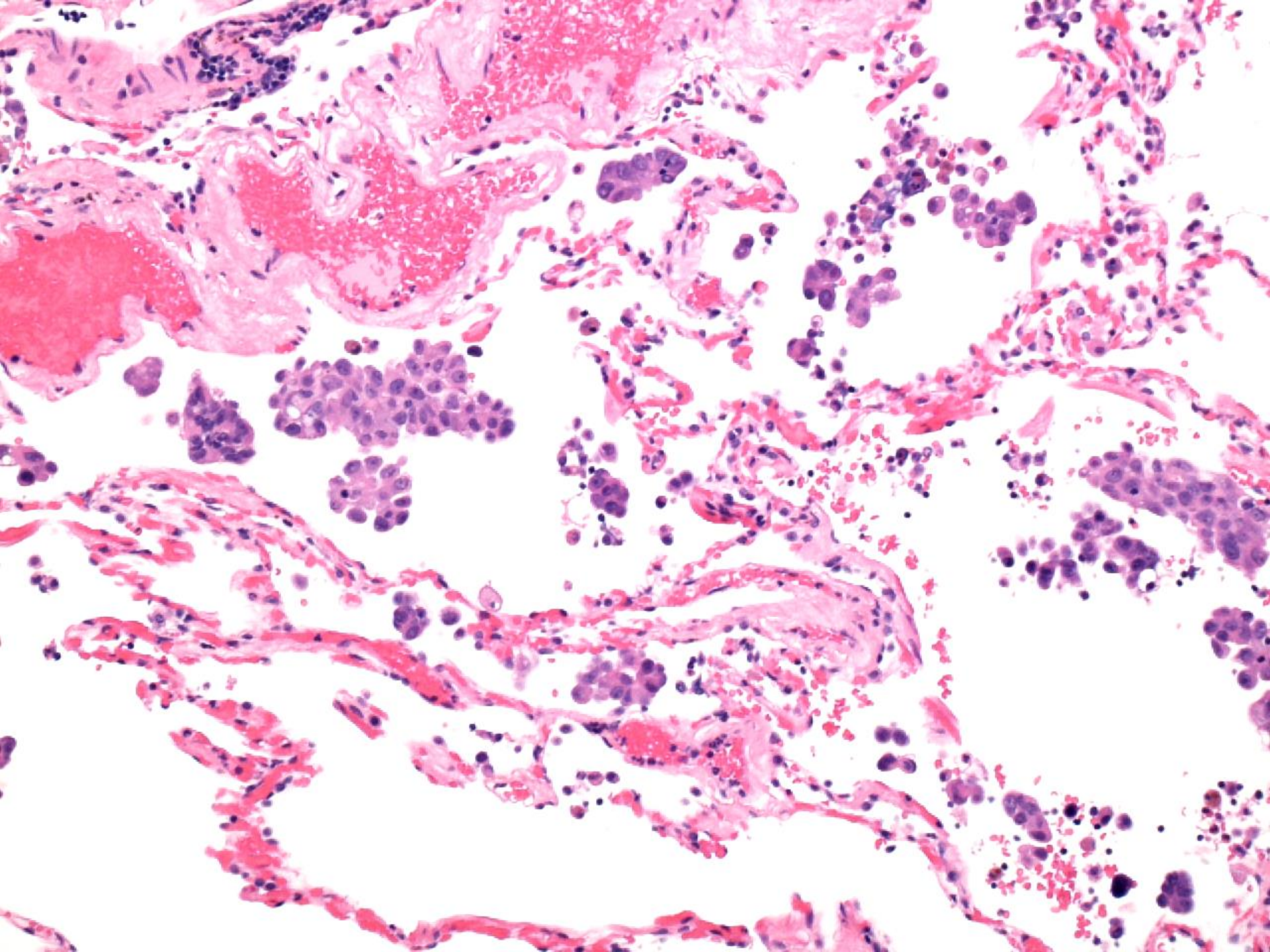


Formerly 'mucinous BAC'

**Invasive mucinous adenocarcinoma**

KRAS mutations very common





Spread  
Through  
Alveolar  
Spaces:

STAS

# Clinical impact

- More biologically meaningful classification
  - AIS rather than BAC, MIA
- Pattern predominance and prognosis
  - Adjuvant therapy?
- Histology – Molecular correlates?
  - Signet ring cells and ALK
  - Invasive mucinous and KRAS
- Histology – radiology correlates
- MIA, STAS, recurrence and sub-lobar resection?

# Squamous Cell Carcinoma

## 1-3A Keratinizing and Non-keratinizing SCC

Squamous cell carcinoma is a malignant epithelial tumour that either shows keratinization and/or intercellular bridges, **or is a morphologically undifferentiated non-small cell carcinoma that expresses immunohistochemical markers of squamous differentiation.**

## 1-3B Basaloid Carcinoma

Basaloid carcinoma is a poorly differentiated malignant epithelial tumour that presents in its pure form as a proliferation of small cells with lobular architecture and peripheral palisading. These cells lack squamous morphology, but show immunohistochemical expression of squamous markers. Tumours with a keratinizing or non-keratinizing squamous cell component, but a basaloid component of > 50%, are also classified as basaloid carcinoma.

## 1-3C Pre-invasive disease

Squamous dysplasia and Carcinoma in situ



# Clinical relevance

- None, other than classification migration and possible effect on post-op survival statistics

# Neuroendocrine tumours

## High Grade Neuroendocrine tumours

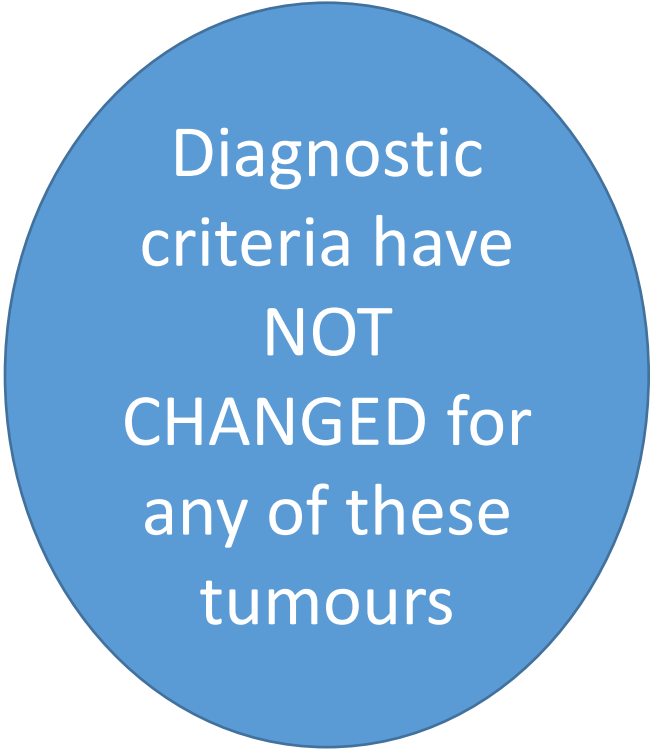
- 1-4A: Small cell carcinoma
- 1-4B: Large cell neuroendocrine carcinoma (LCNEC)

## Low Grade Neuroendocrine tumours

- 1-4C: Carcinoid tumours
  - Typical Carcinoid
  - Atypical Carcinoid

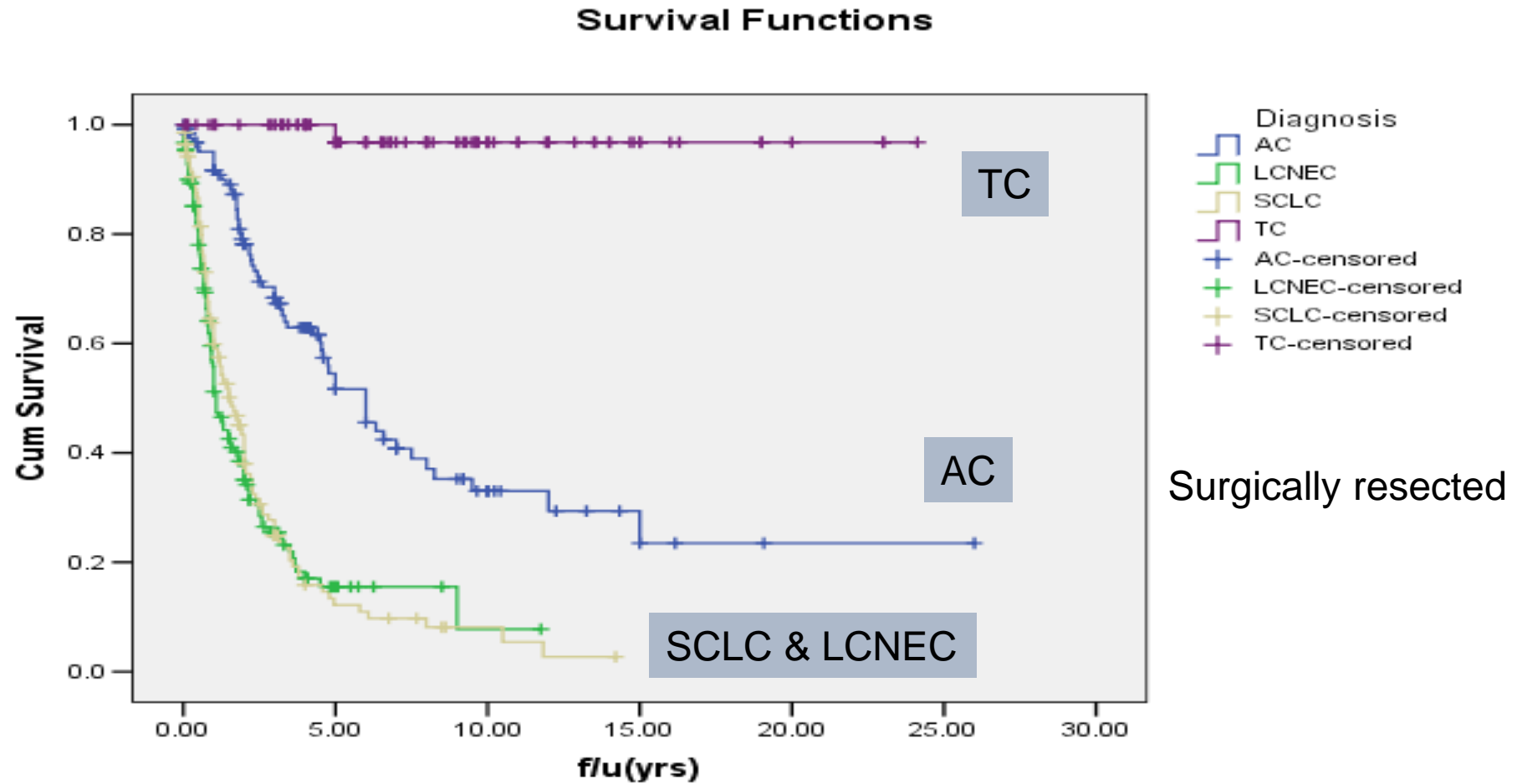
## Precursor lesion

- 1-4D: Diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH)



Diagnostic  
criteria have  
**NOT**  
**CHANGED** for  
any of these  
tumours

# LUNG NE TUMORS: SURVIVAL



510 AFIP Cases: TC-92; AC-127, LCNEC – 152, SCLC – 139;  $p < 0.0001$ . Data courtesy of WD Travis.

# Clinical Impact

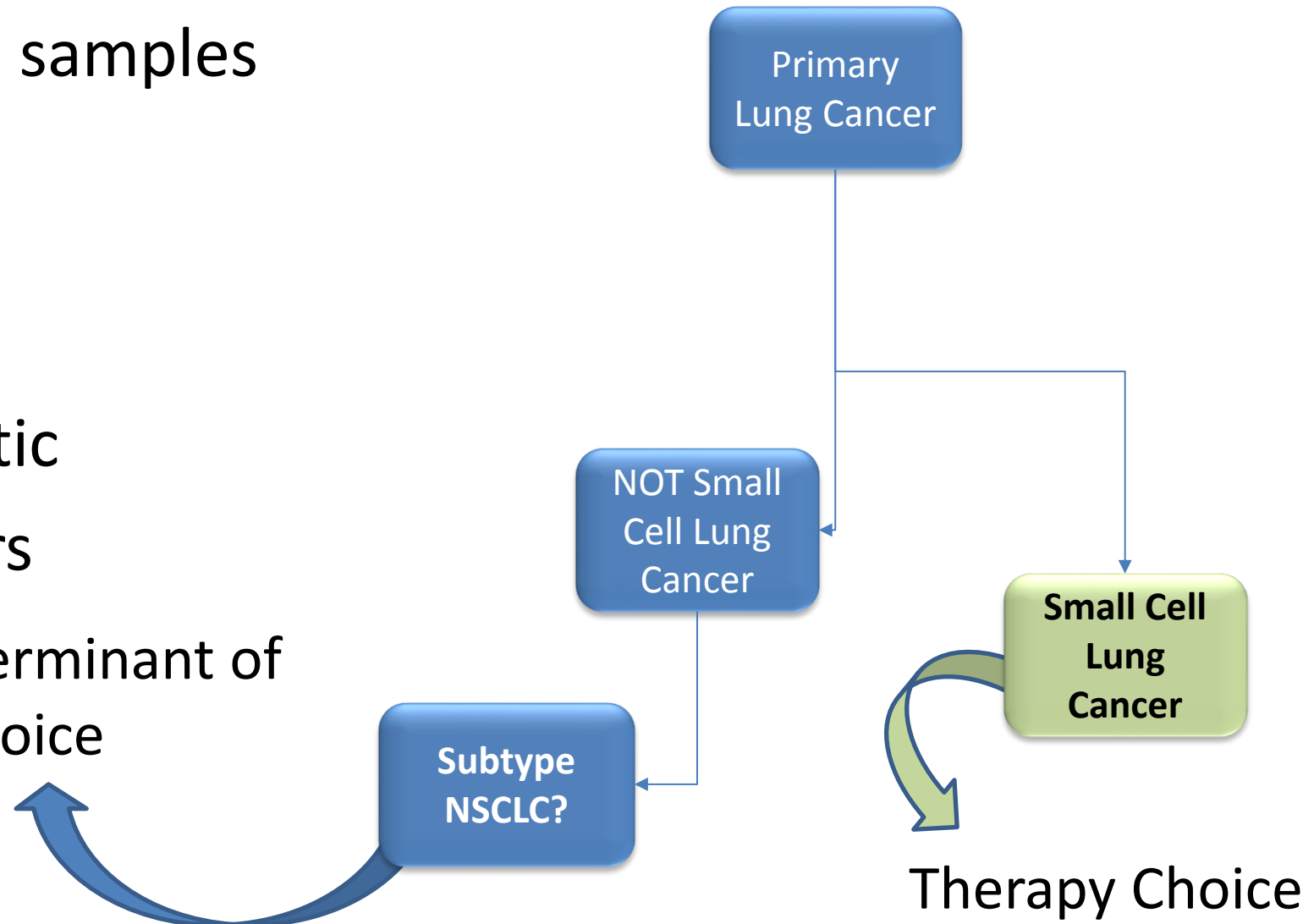
- Can LCNEC now be regarded more like SCLC, rather than NSCLC?

# Clinical requirements of diagnosis: Advanced Disease

Advanced disease, small samples

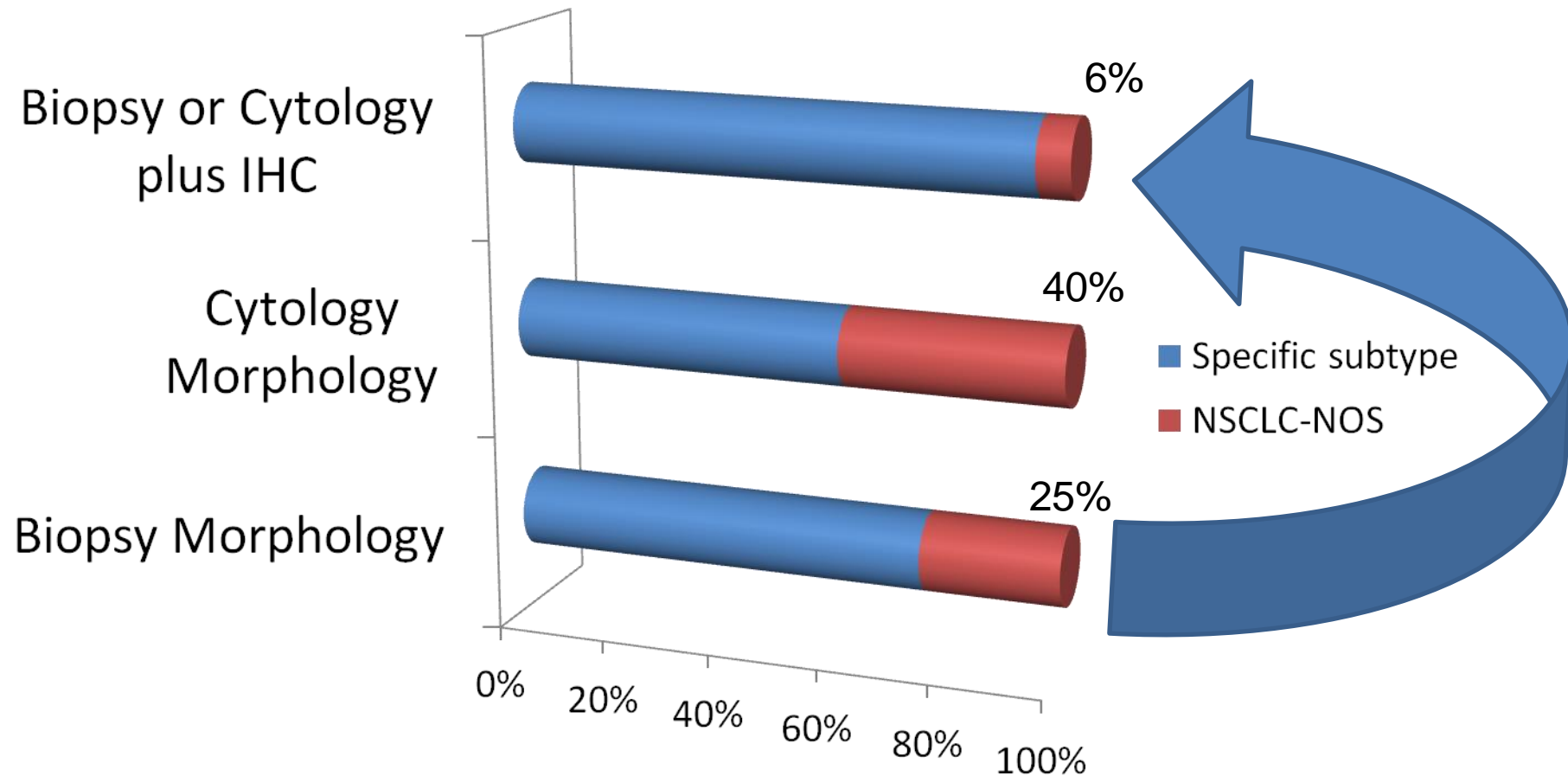
- WHO 2004 *et prev*
  - inapplicable
  - inaccurate
- NSCLC-NOS problematic
- NSCLC subtype matters

Now a critical determinant of  
Therapy Choice





# Subtyping NSCLC greatly improved by IHC



- Predictive IHC has 'levelled the playing field'
- Better diagnosis possible on poorer specimens

# Diagnosis of NSCLC in small biopsy & cytology

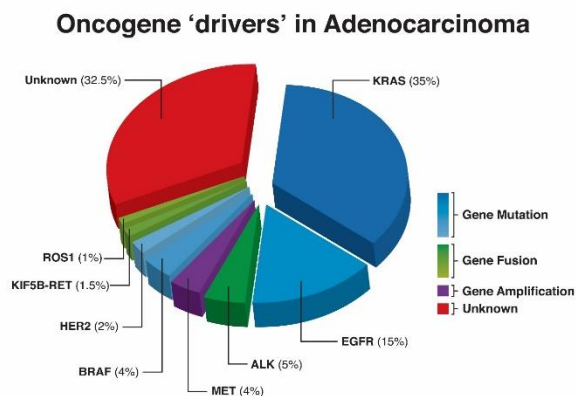
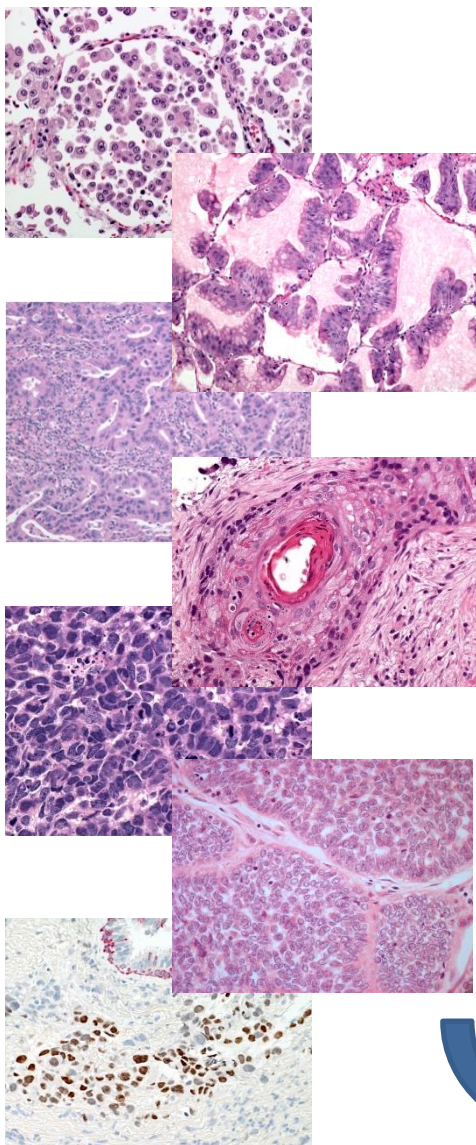
- Squamous cell carcinoma
- NSCLC, probably squamous cell (IHC – p40, p63, CK5/6)
- Adenocarcinoma
- NSCLC, probably adenocarcinoma (IHC – TTF1)
- NSCLC-NOS – cannot be resolved (null IHC)
- Occasionally, rare specific types may be suggested

# Clinical Impact

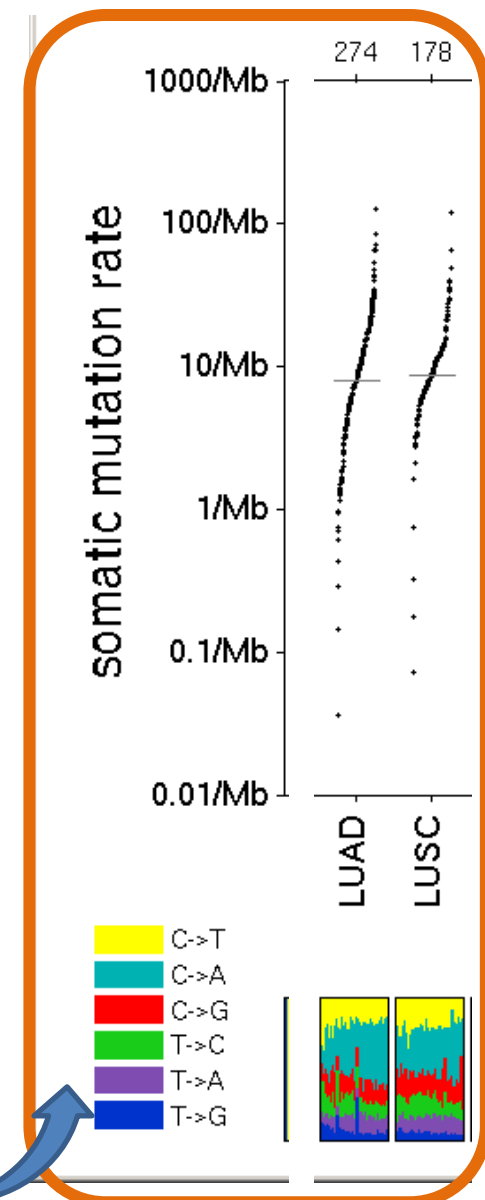
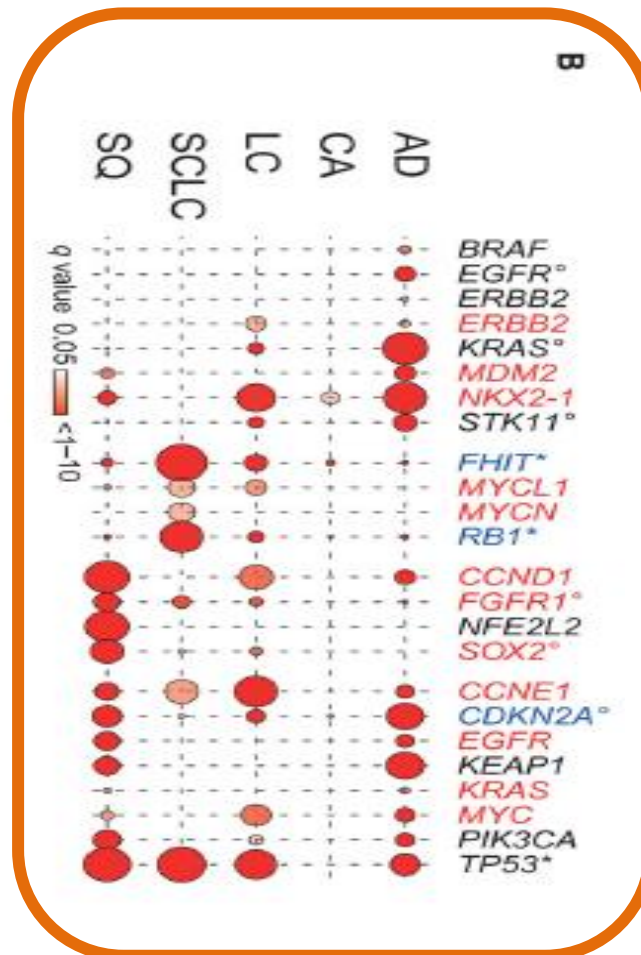
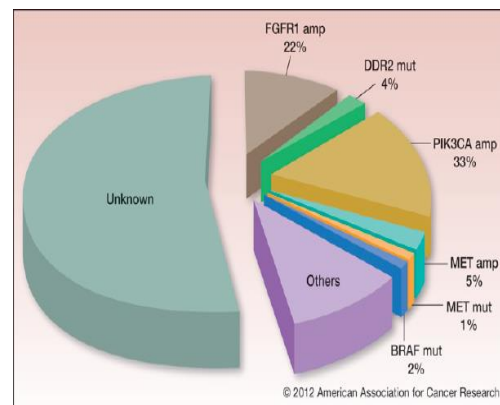
- Substantial
- Therapeutic selection – efficacy and toxicity
- Triage for molecular testing
- Incorporation into clinical trial data collection?



# Genetic profiles, Liquid biopsies & Molecular microscopes?



**Oncogene 'drivers' in Squamous carcinoma**



# Clinical impact of the WHO 2015 classification

- Case reassignment might impact post-operative survival data
- Better prognostication in resected adenocarcinoma
- Possible challenges posed by pathological factors which could influence surgery
- Better 'home' for Neuroendocrine tumours
- Better diagnosis on small samples
- Assimilation of genetic data into the way we regard individual patients and their lung cancers