Lung Adenocarcinoma Variants – a Source of Headaches

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Disclosures

The presenter has indicated that they have a relationship which in the context of their presentation, could be perceived as a real or apparent conflict of interest but do not consider that it will influence their presentation. The nature of the conflict is listed:

Affiliation / Financial interest	Commercial Company
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Advisory board member	Sanofi
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Participation in a company sponsored bureau:	None
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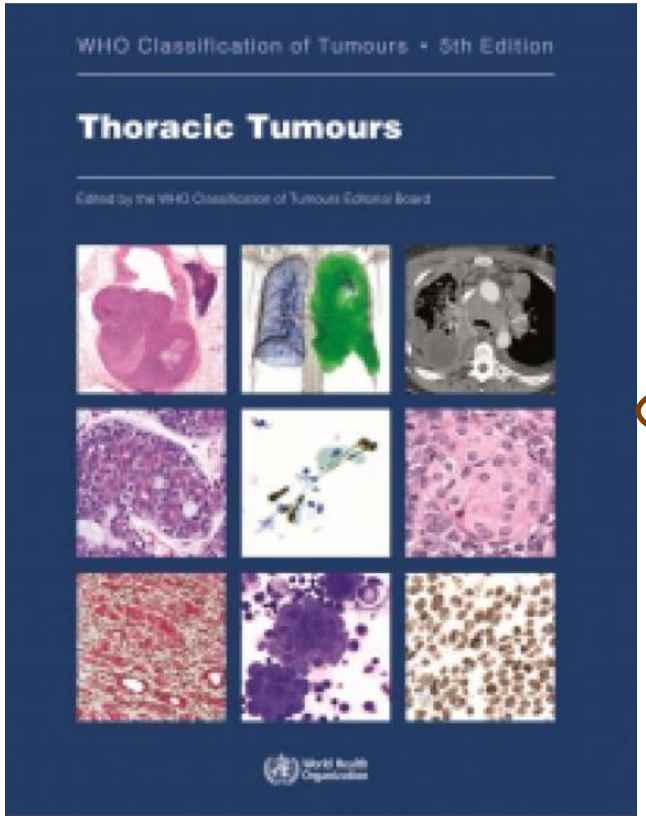


2. Tumours of the lung

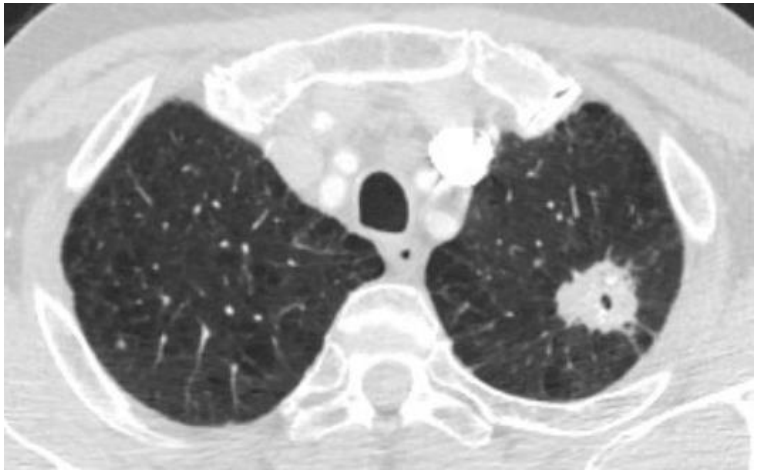
Adenocarcinoma variants

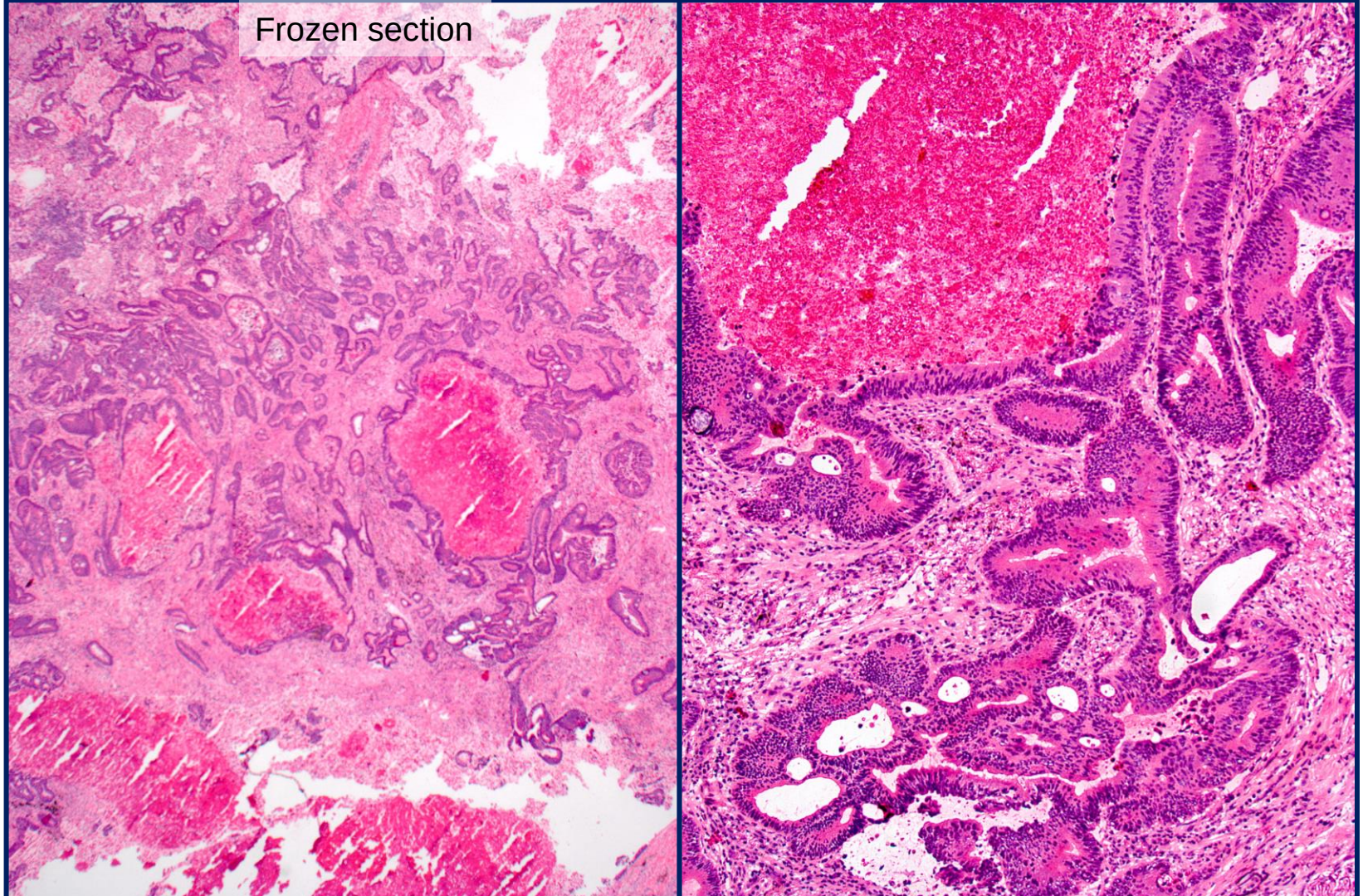
Adenocarcinoma Variants

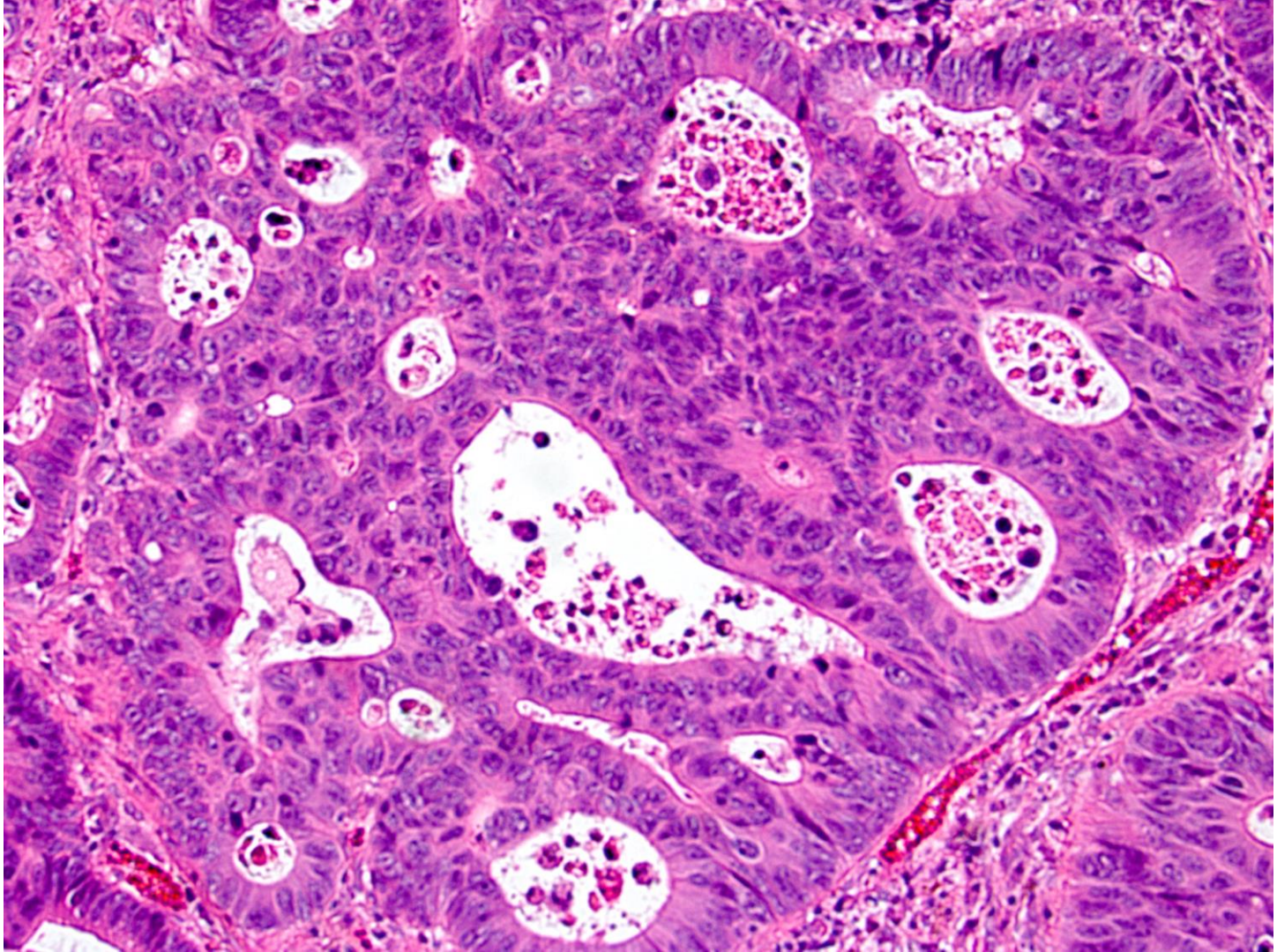
- Invasive mucinous adenocarcinoma
- Colloid adenocarcinoma
- Enteric-type adenocarcinoma
- Fetal adenocarcinoma

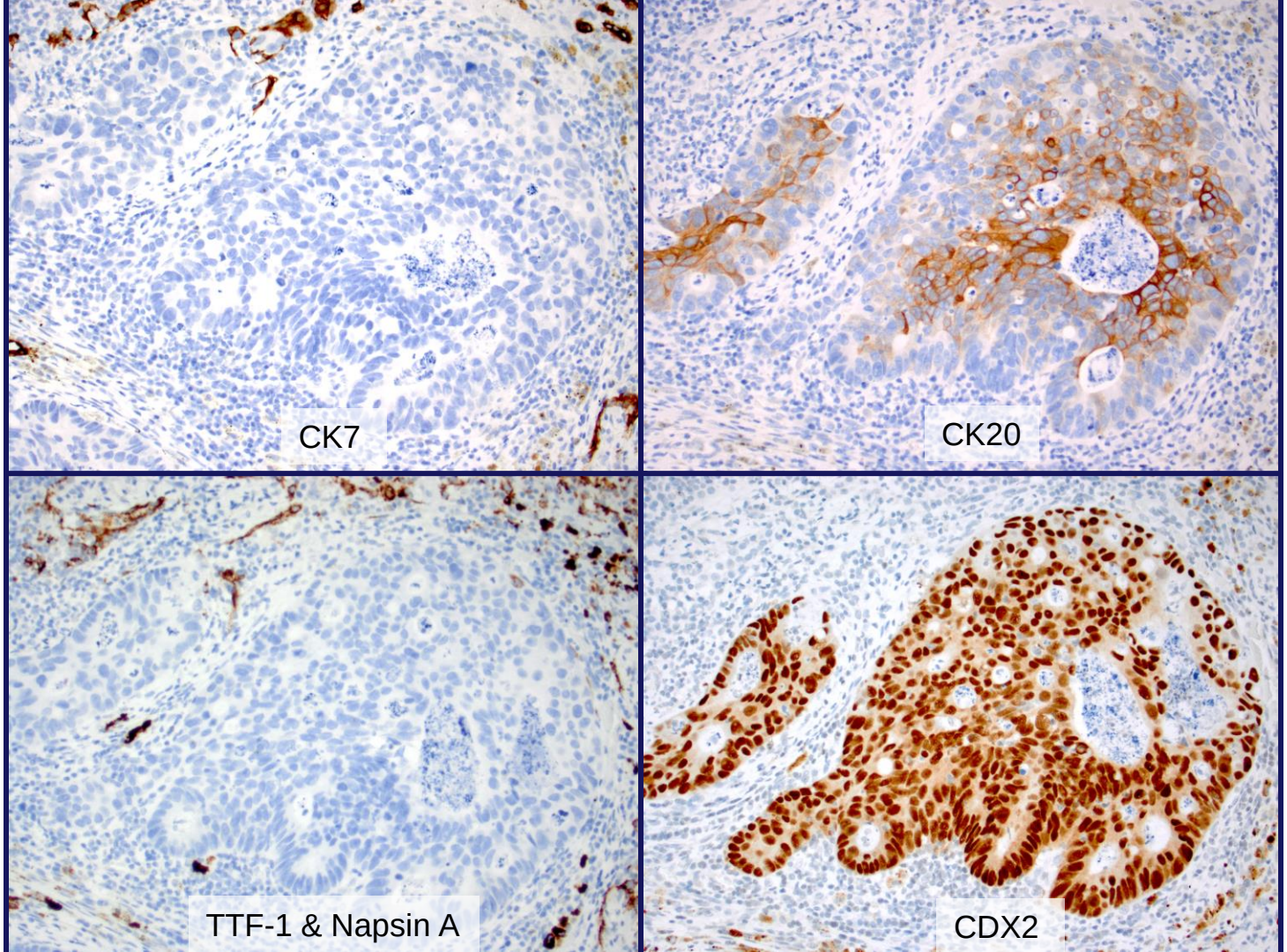
77-year-old male, former smoker

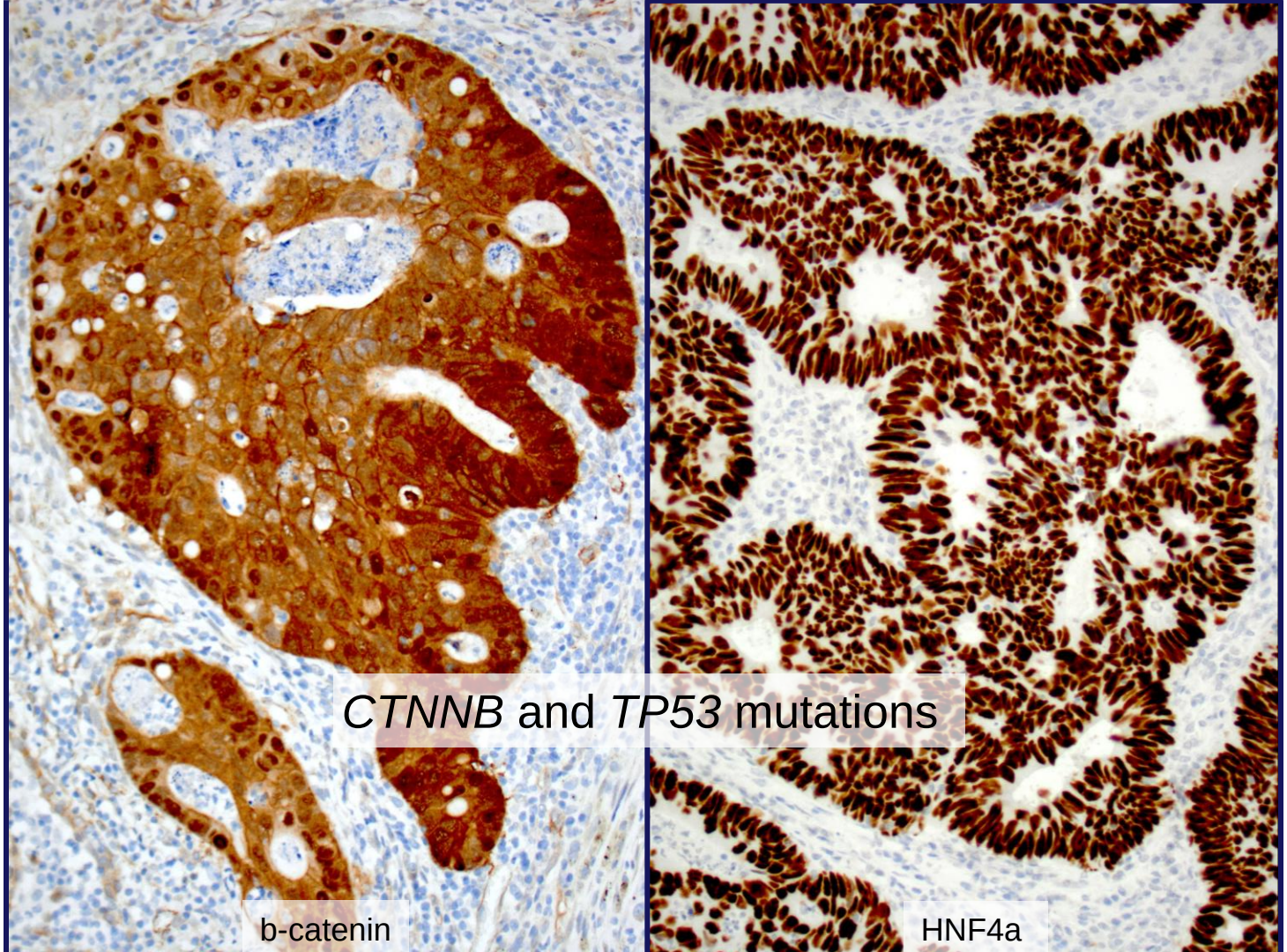
- History of Stage I sigmoid colon cancer resected in 2003
- Presented with an incidentally found, 2.7 cm solitary lung nodule
- No symptoms




Frozen section




CK7
CK20
TTF-1 & Napsin A
CDX2


CTNNB and *TP53* mutations
b-catenin
HNF4a

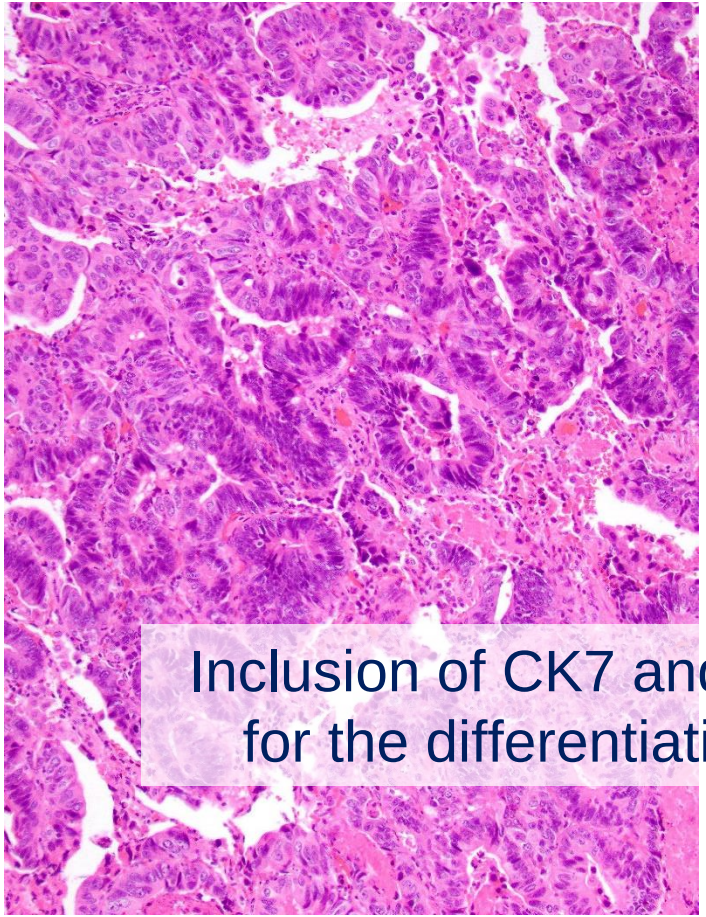
Case Continued …

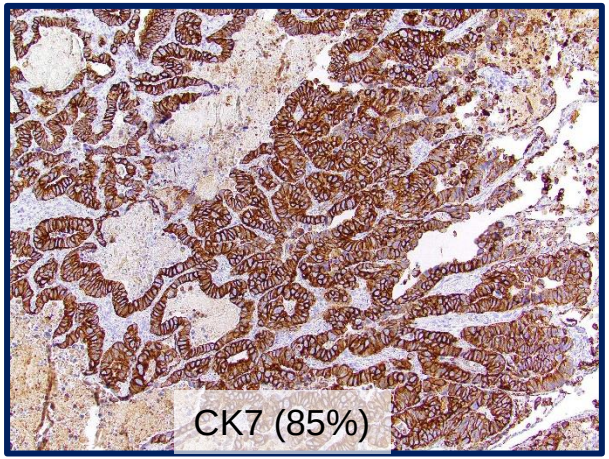
- Metastasis form a colonic primary favored
- The original CRC was a polypoid stage I tumor in 2003
- The patent underwent lower GI endoscopy that was negative
- No recurrence in several years after the wedge resection
- Still ? lung primary vs. met from colon

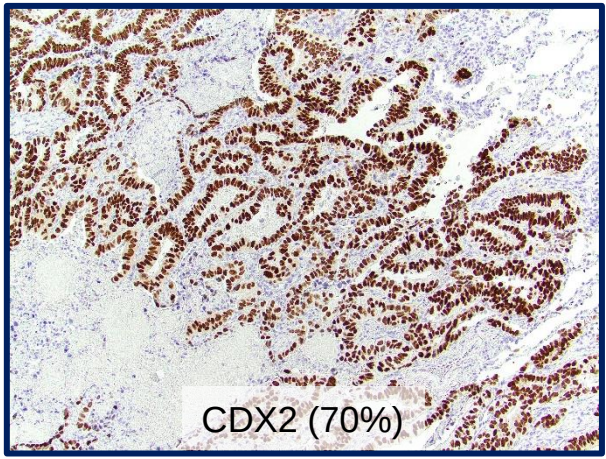
Enteric Type Adenocarcinoma

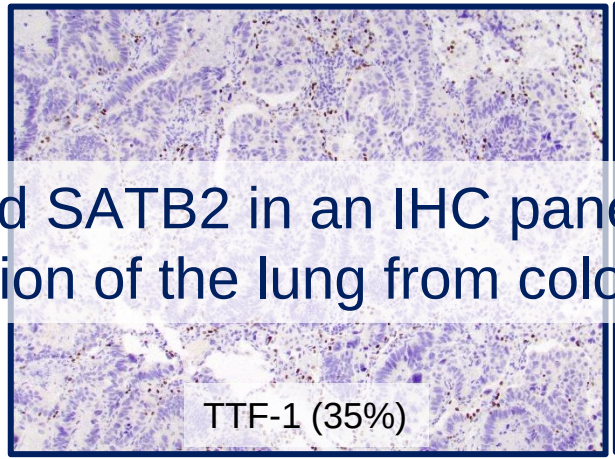
- Defined as an adenocarcinoma resembling colorectal adenocarcinoma (enteric pattern in ≥ 50% of the tumor)
- Expression of at least one intestinal marker
- The diagnosis requires careful clinical evaluation to exclude a colorectal primary
- *KRAS* mutations more frequent in this entity than conventional lung adenocarcinoma
- Share the similar molecular profile with the colonic counterpart except *APC* mutations
- No consistent data on prognosis

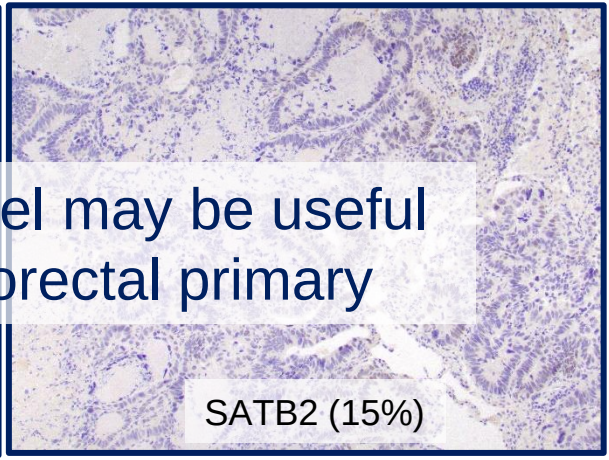
Immunoprofile of enteric-type adenocarcinoma of the lung





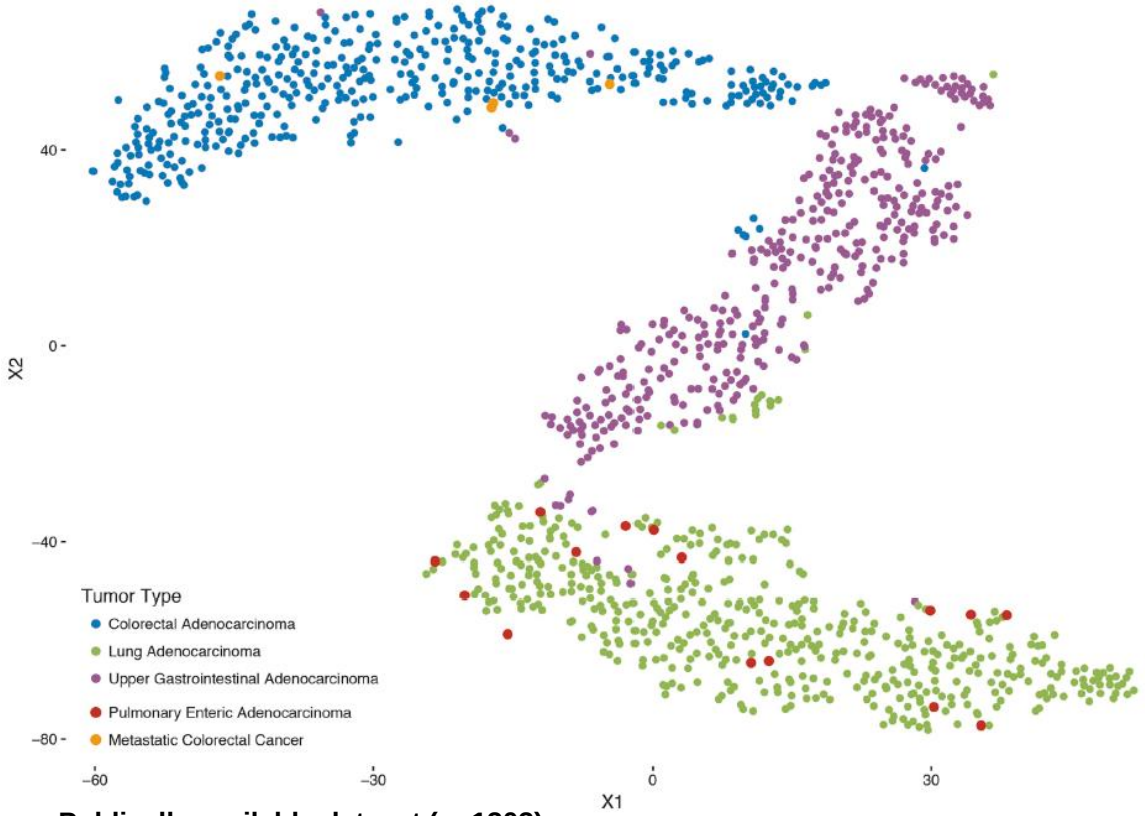






Inclusion of CK7 and SATB2 in an IHC panel may be useful for the differentiation of the lung from colorectal primary

DNA methylation profiling reliably distinguishes pulmonary enteric adenocarcinoma from metastatic colorectal cancer

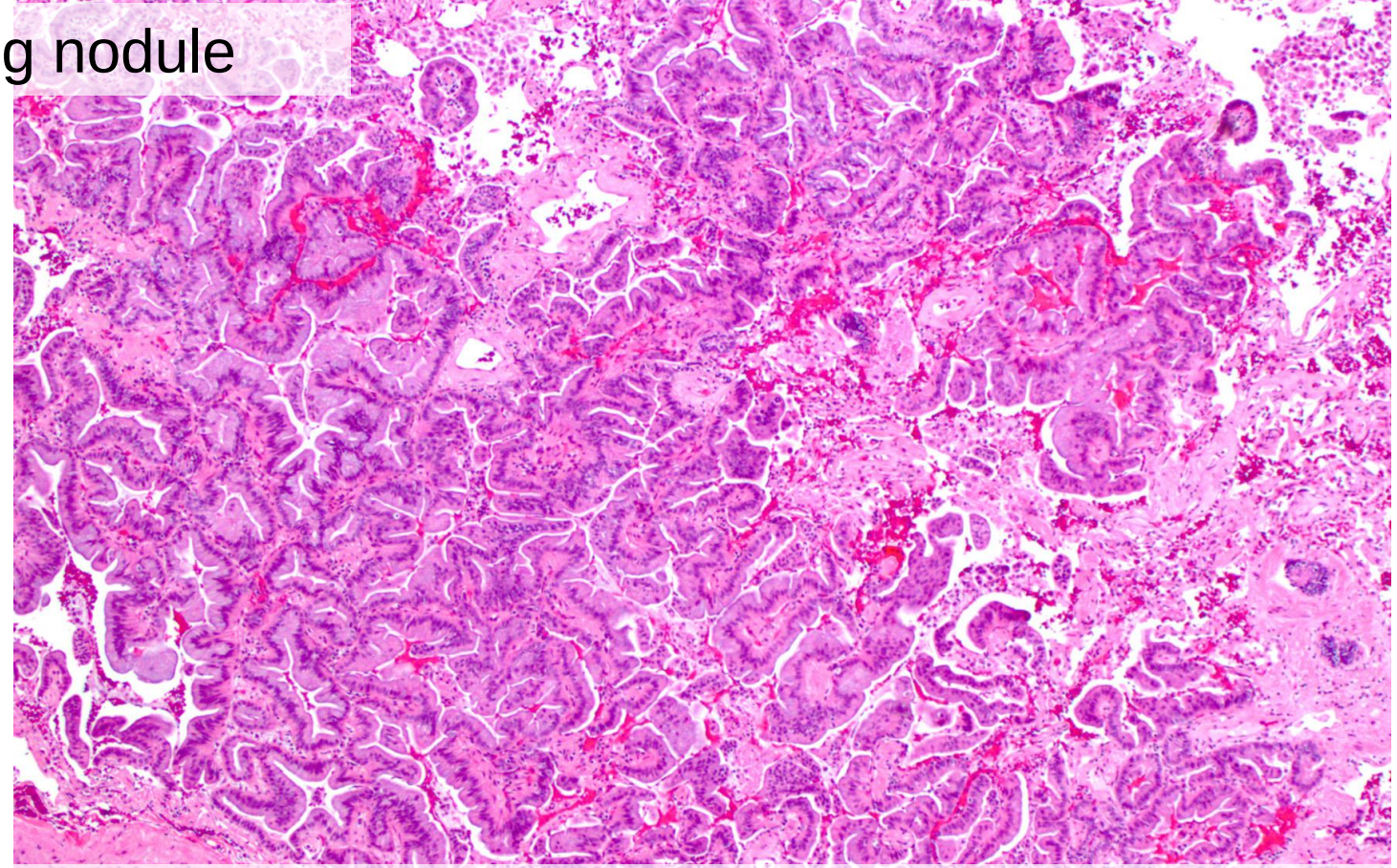


Publically available dataset (n=1303)

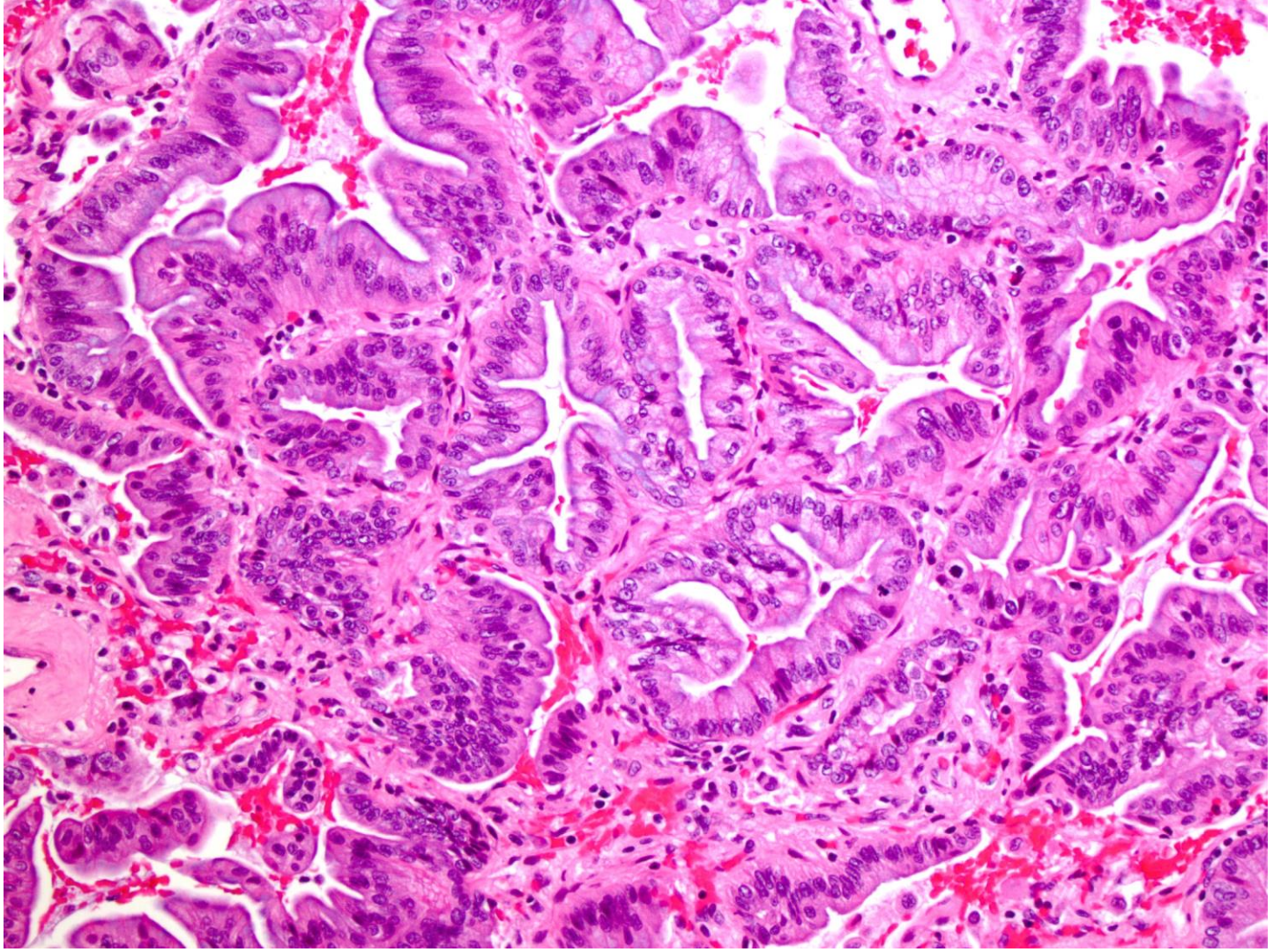
- A machine learning algorithm was trained to identify the correct tumor type in a reference cohort (n=600)
- The resulting classifier correctly classified all specimens as pulmonary, colorectal or upper GI carcinomas in a validation cohort (n=680)
- The classifier accurately classified 15 pulmonary enteric adenocarcinomas, 4 primary colorectal carcinomas and 4 metastatic colorectal carcinomas in surgical specimens

Jurmeister, et al. Modern Pathol 2019;32:855-63

Lung nodule

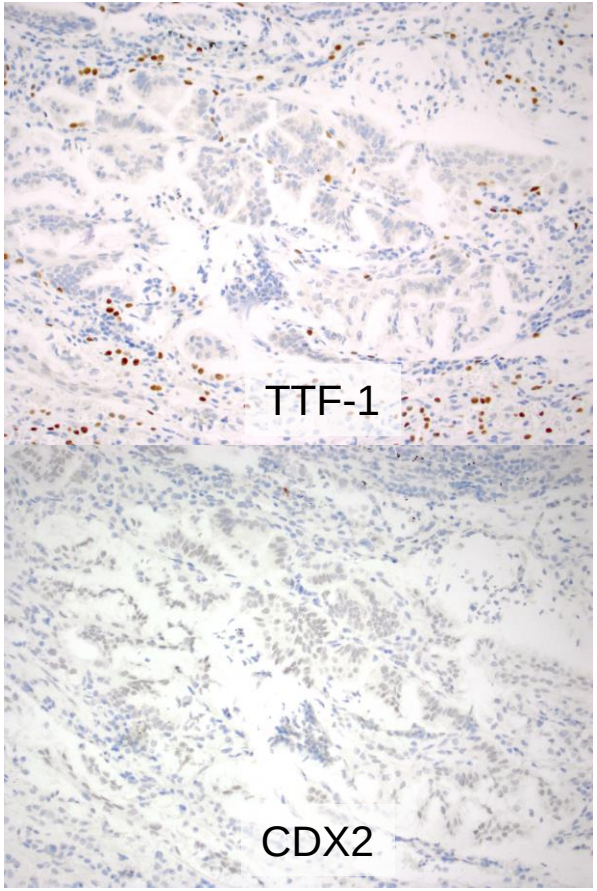


74 y.o. lady with a 3.5 cm pancreatic mass
and a 1.3 cm single lung nodule

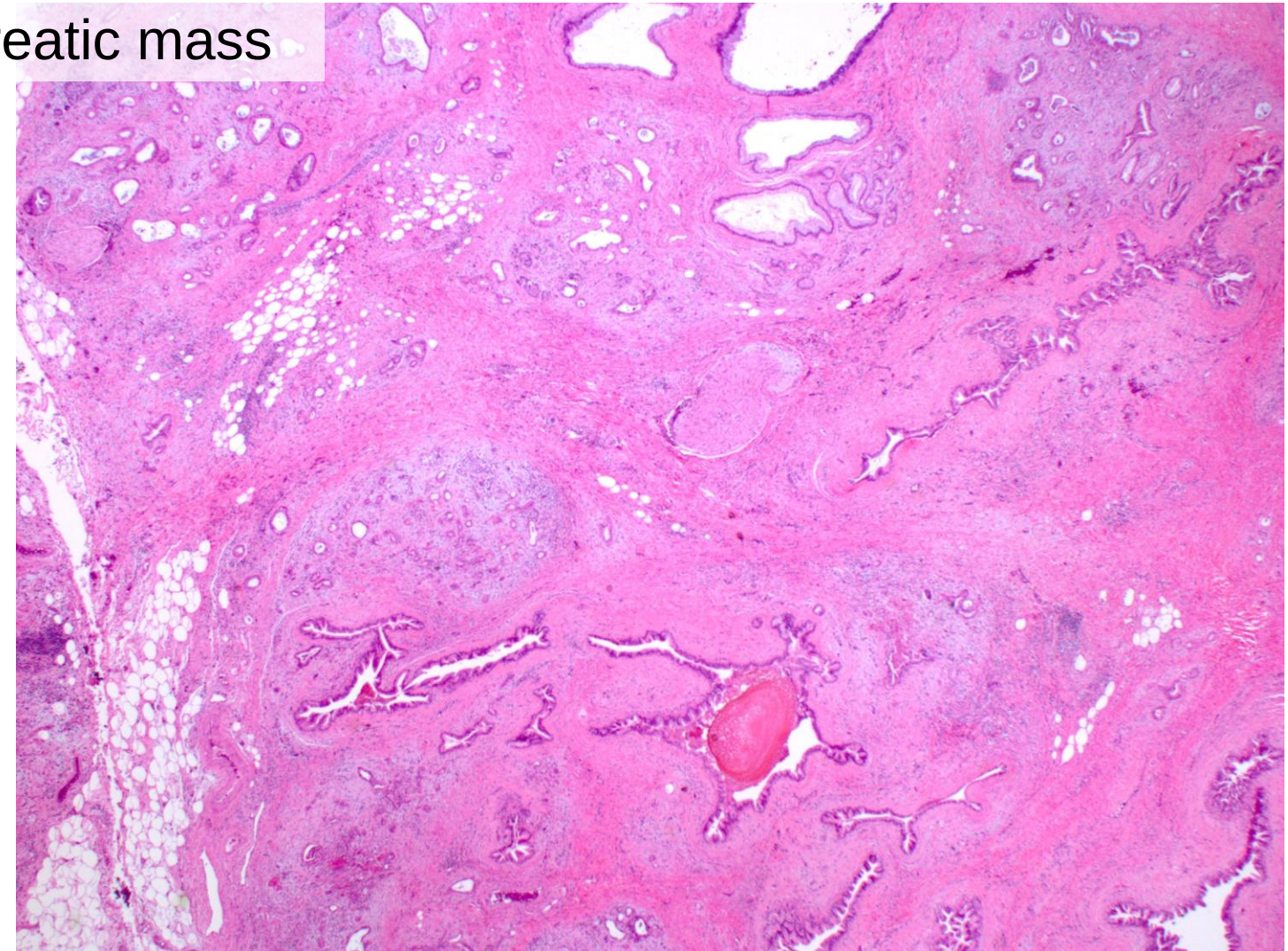


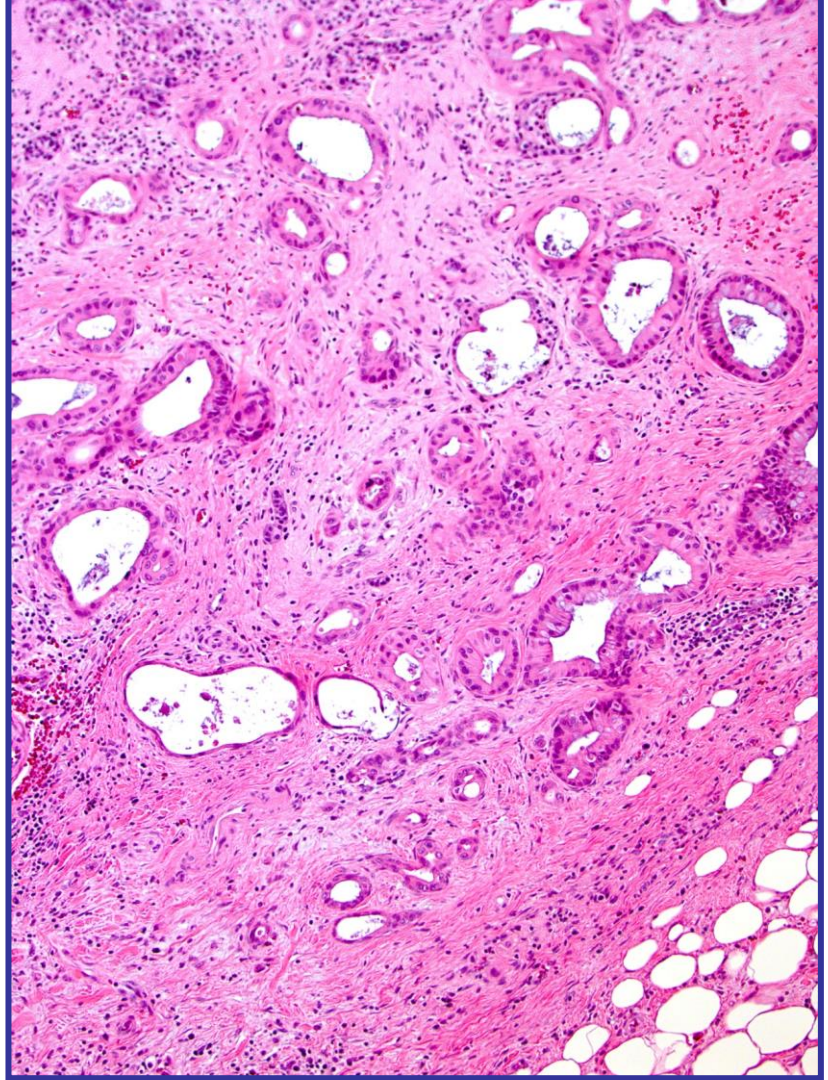
Lung Nodule IHC Results

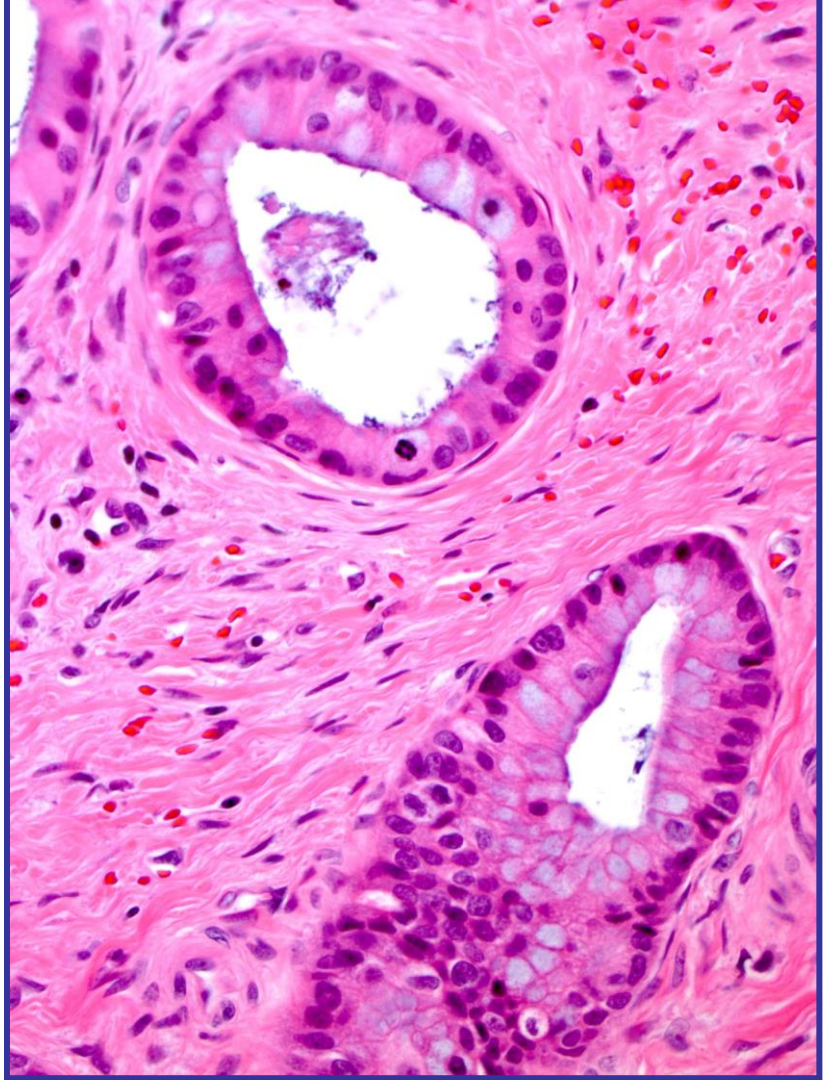
- CK 7 +ve
- CK19 +ve
- CK20 -ve
- TTF1 -ve
- Napsin A -ve
- CDX2 weakly +ve
- CA19-9 +ve, focal
- CA125 +ve, focal
- MUC1 +ve
- MUC2 -ve



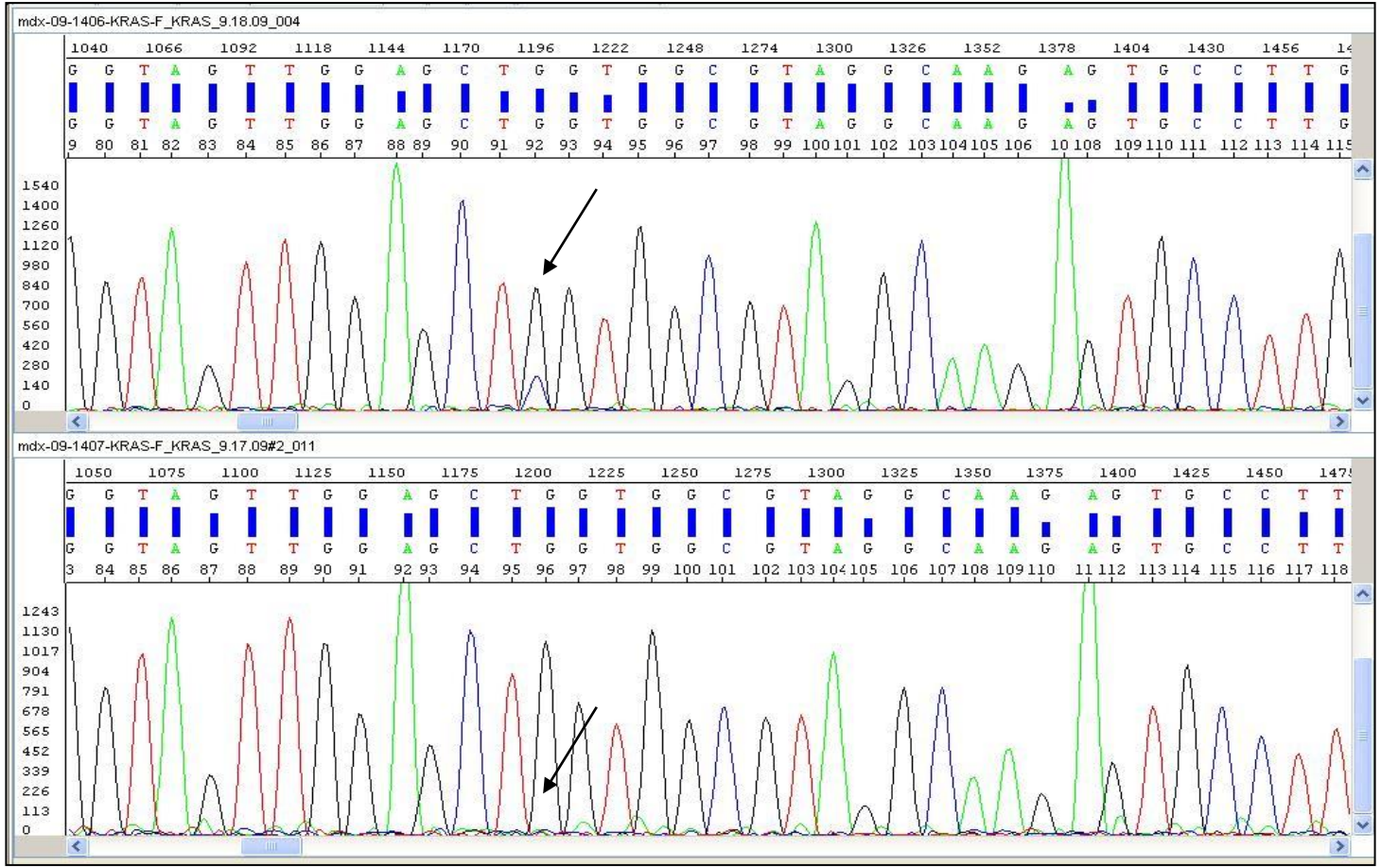
Pancreatic mass







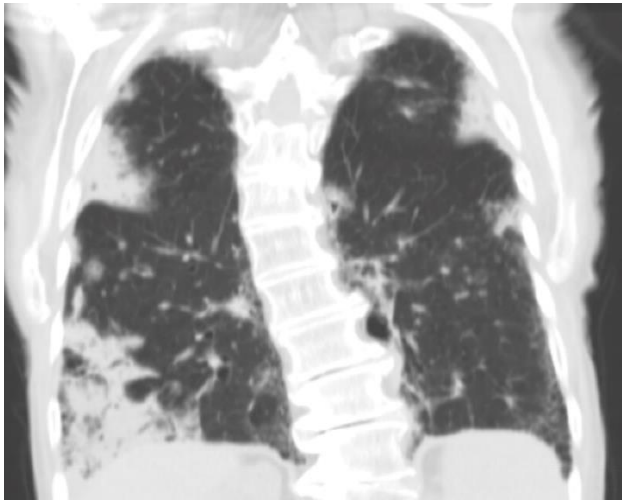
Lung: 12GGT>CGT (nucleotide change 34G>C; *KRAS G12R*)



Pancreas: 12 GGT>CGT (nucleotide change 34G>C; *KRAS G12R*)

Invasive Mucinous Adenocarcinoma (IMA)

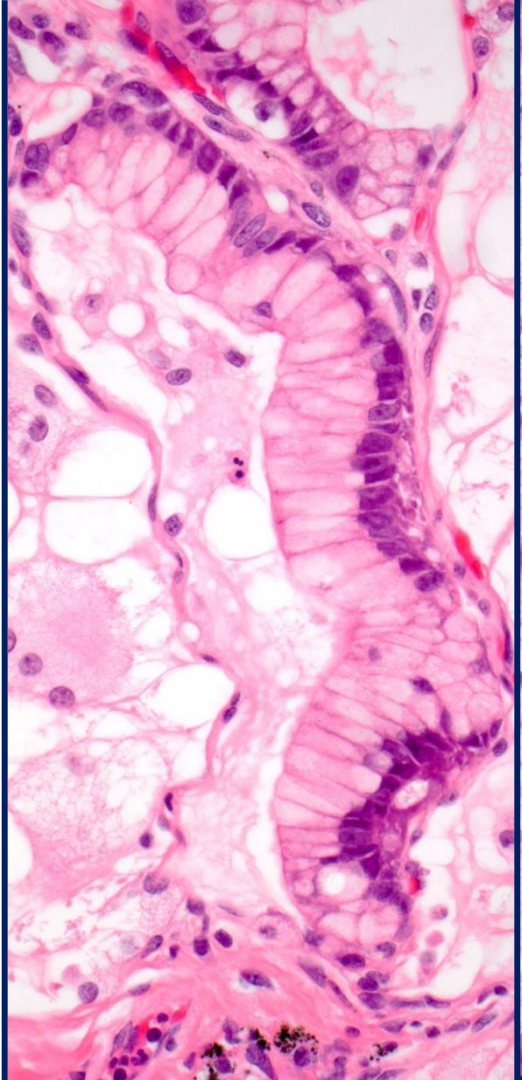
- Primary lung adenocarcinoma with tumor cells exhibiting a goblet or columnar morphology, abundant intracytoplasmic mucin and basally oriented nuclei
- Reported prevalence in resected cohorts is approximately 5% (3-10%)
- Approximately 55% of cases occur in females
- Frequently associated with exposure to tobacco smoking
- Tend to present with multi-centric opacities or consolidation and multi-lobar and bilateral involvement, mimicking pneumonia



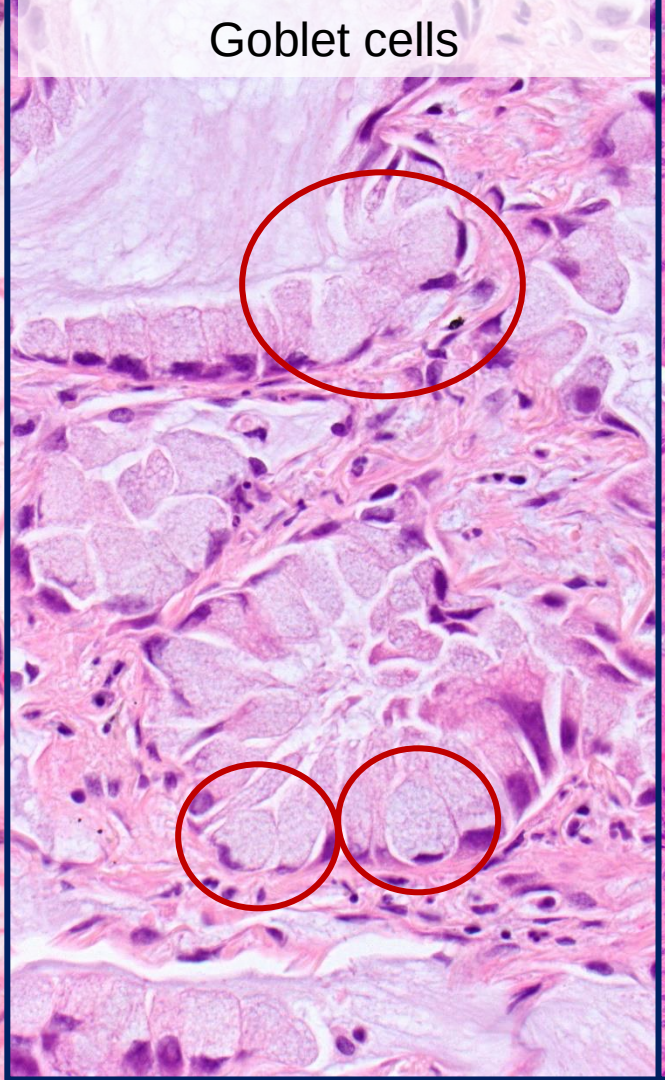
Consolidations with air-bronchogram in a multi-lobar and bilateral distribution, mimicking pneumonia

Cytomorphology of IMA

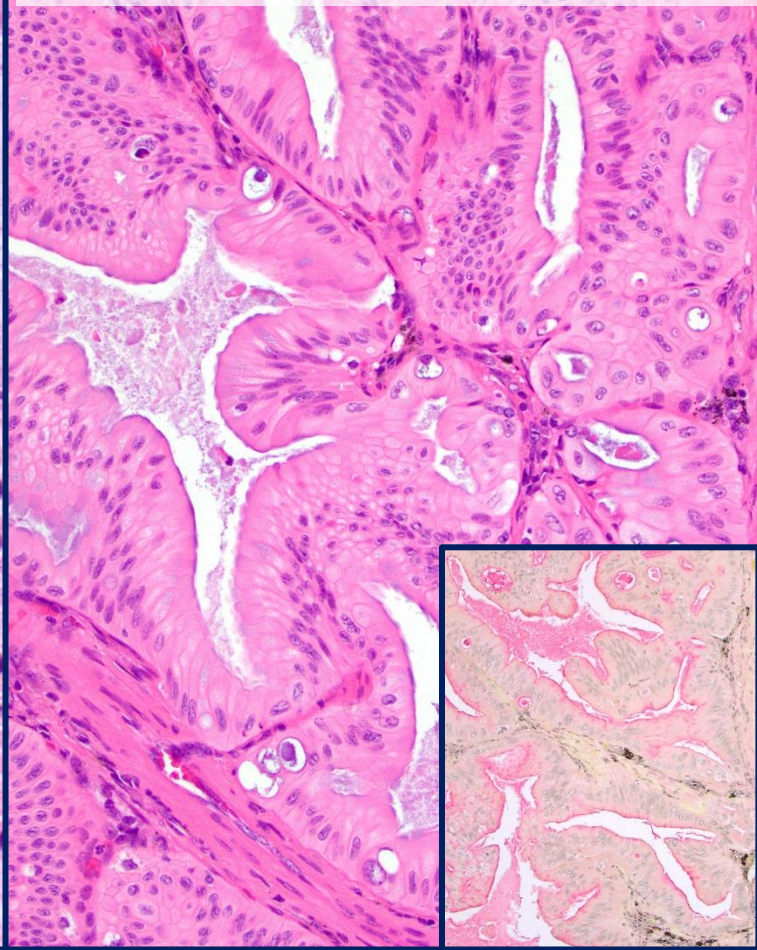
- A goblet or columnar morphology with abundant intracytoplasmic mucin
- Basally oriented nuclei usually with inconspicuous or absent nuclear atypia
- Lepidic-predominant growth is common, but usually invasive foci, including acinar, papillary, micropapillary, solid and/or cribriform growth pattern are present
- The invasive component of IMA often exhibits less intracytoplasmic mucin than lepidic component
- Mixed mucinous/non-mucinous morphology (each component $\geq$10%) may be seen
- AIS, mucinous and MIA, mucinous exist, but rare

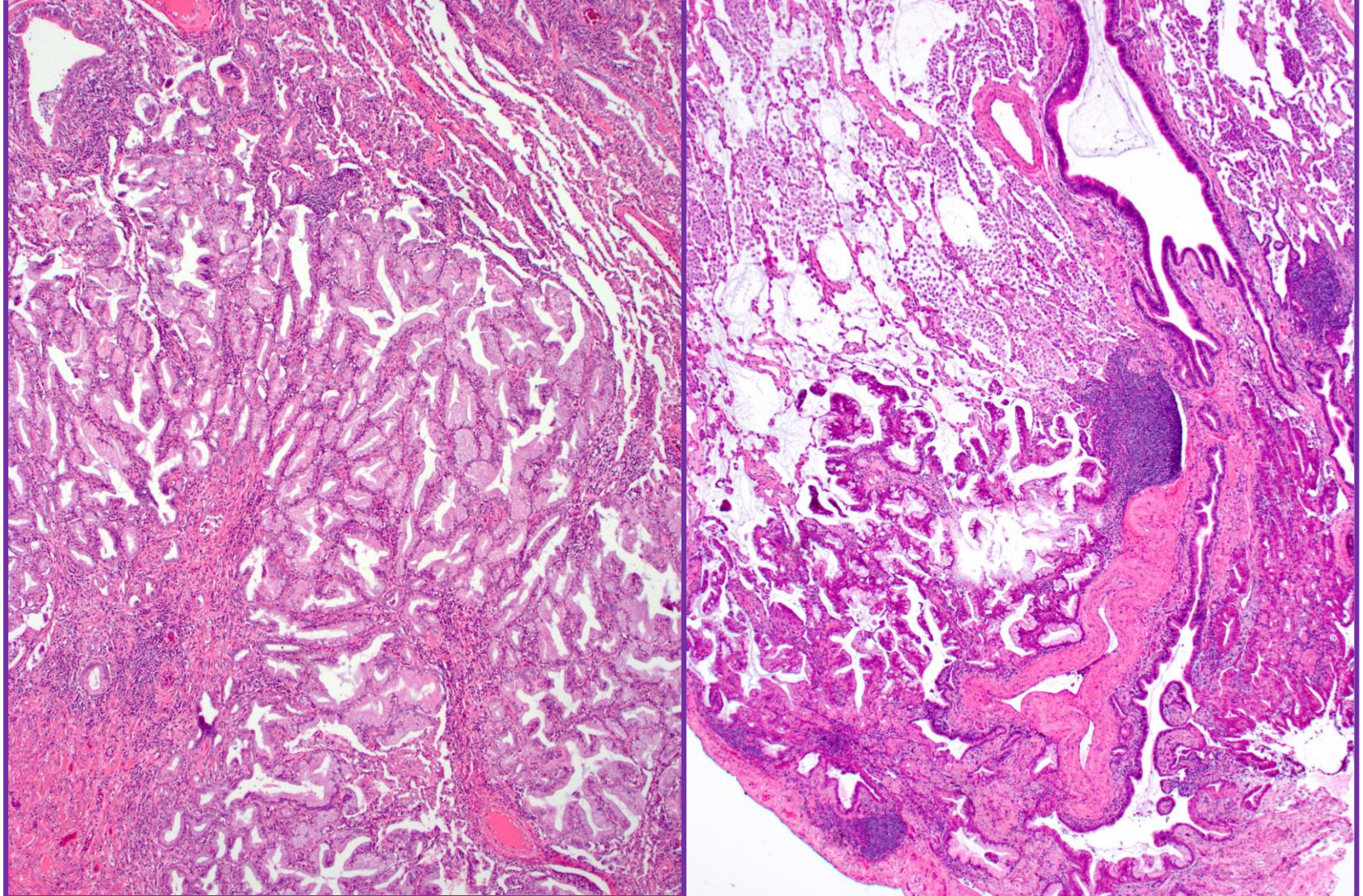


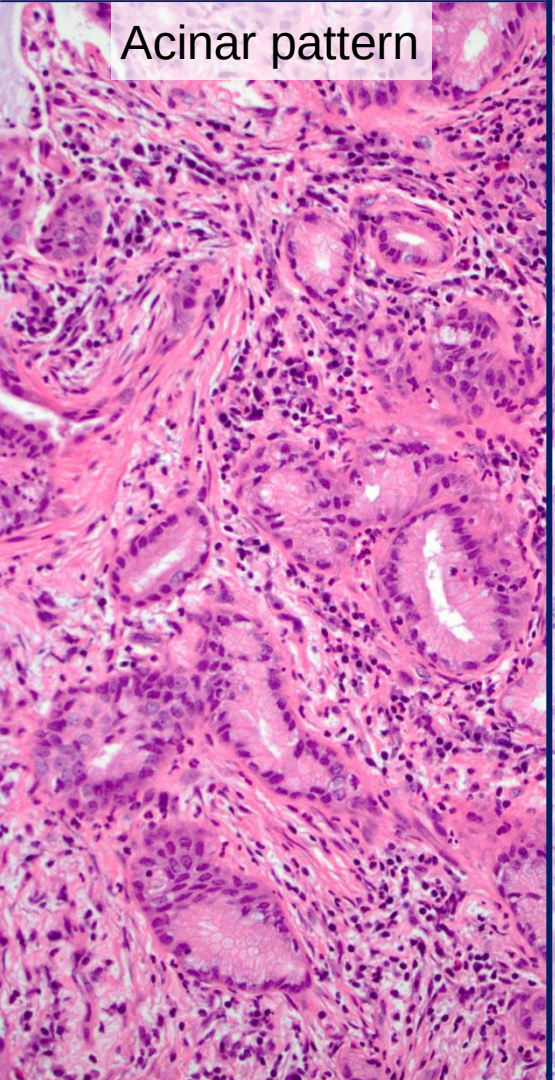
Goblet cells

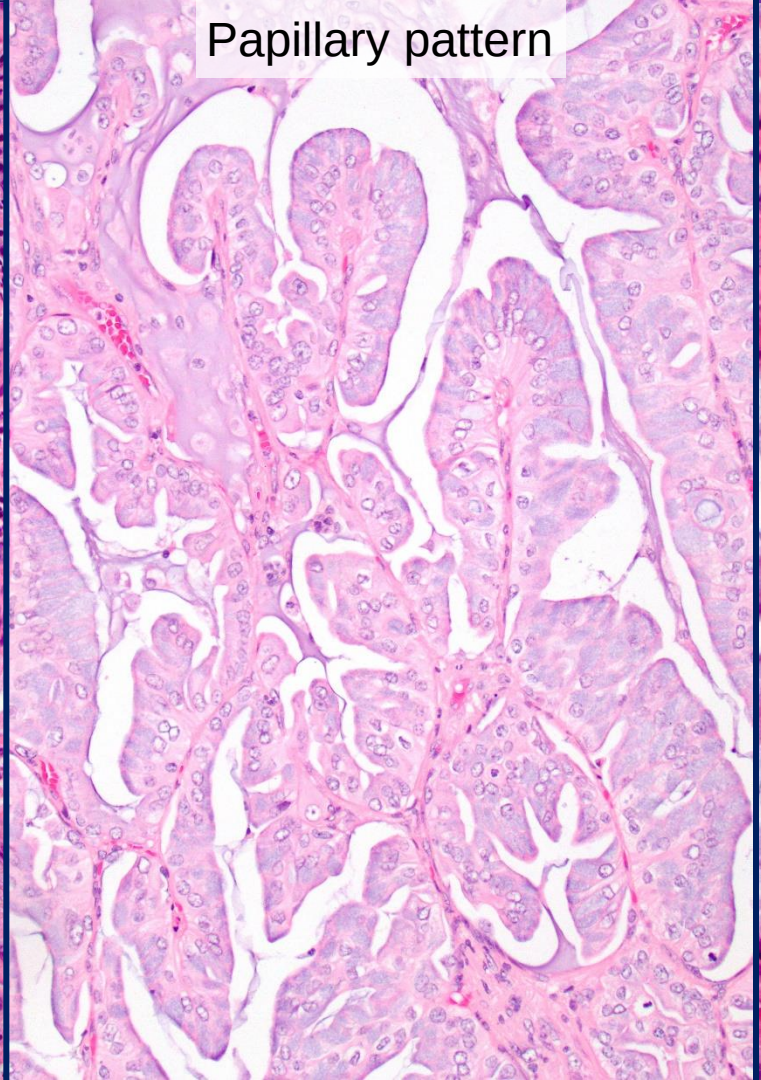


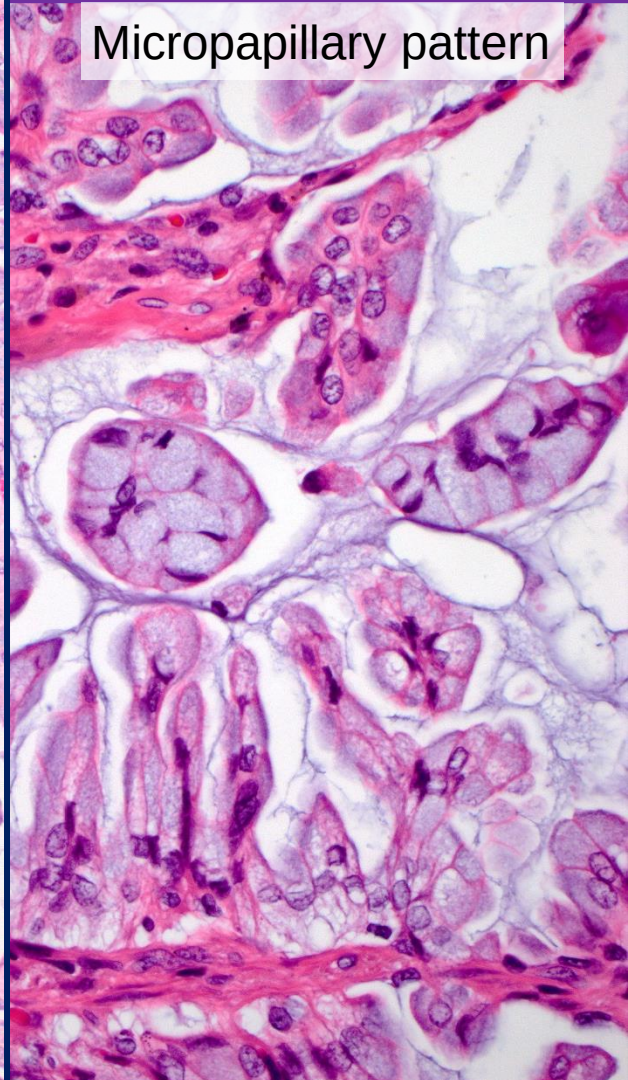
Columnar cells w/ eosinophilic cytoplasm and apical mucin

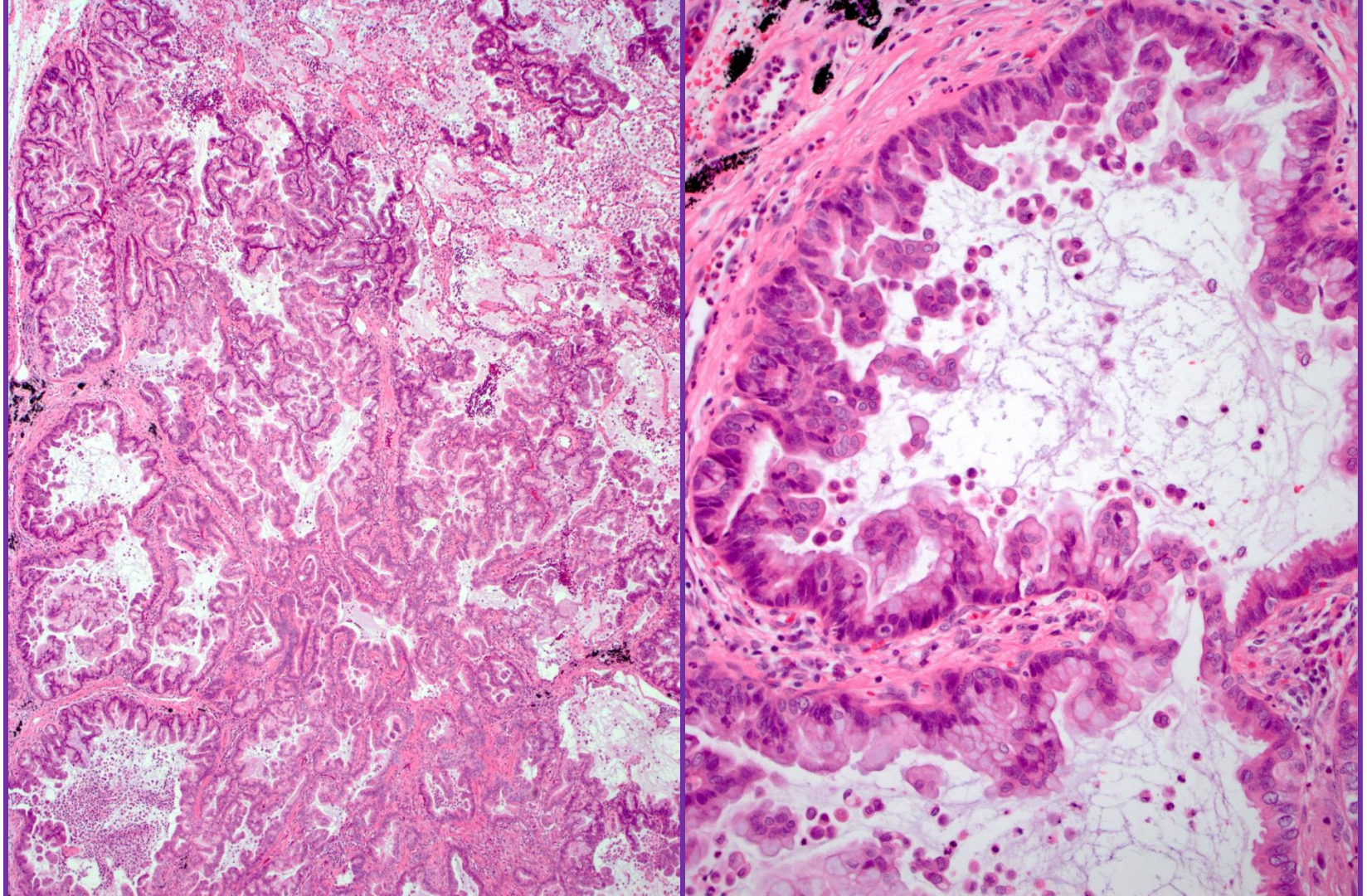




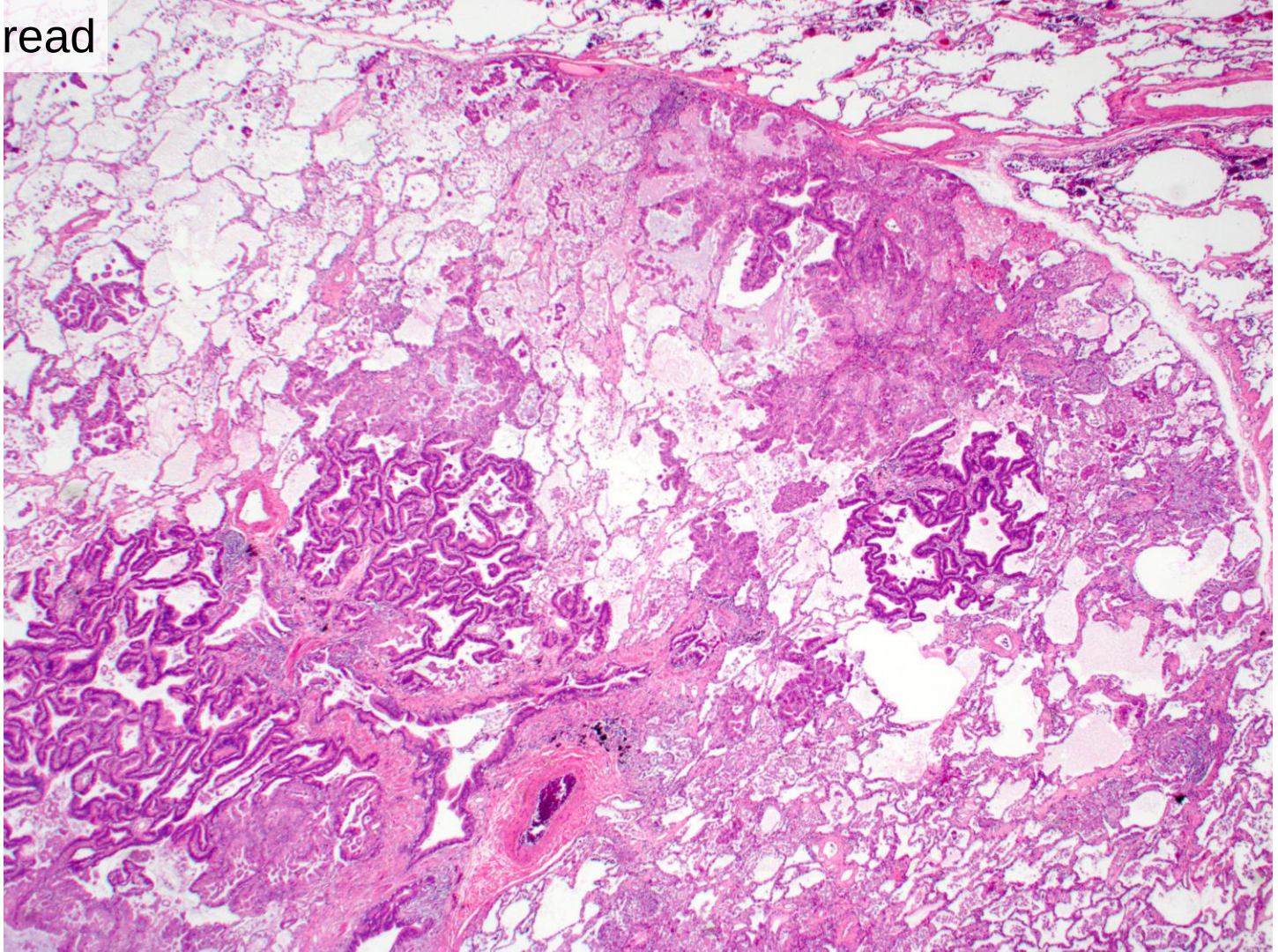

Acinar pattern


Papillary pattern

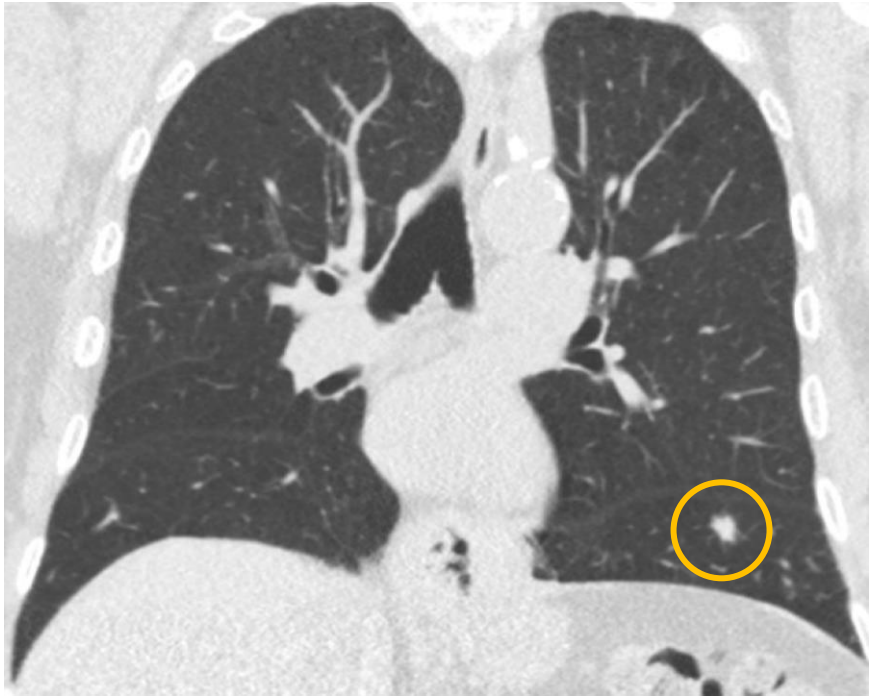

Micropapillary pattern



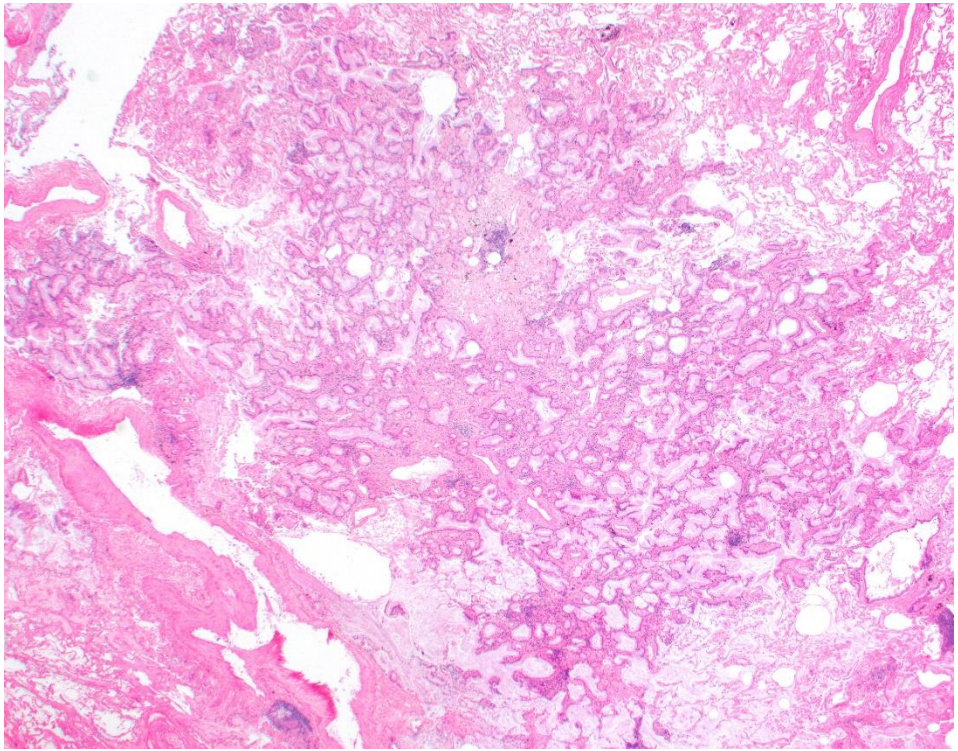
Miliary spread



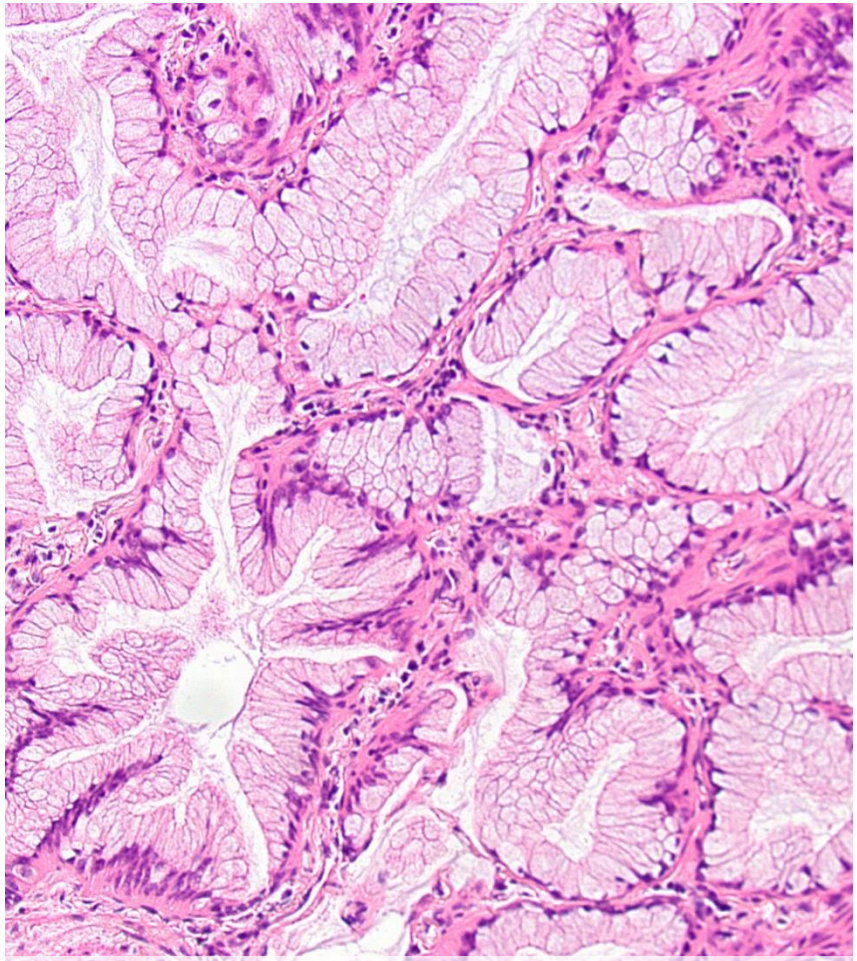
65-year-old male smoker with a small nodule in left lower lobe found through low dose CT screening



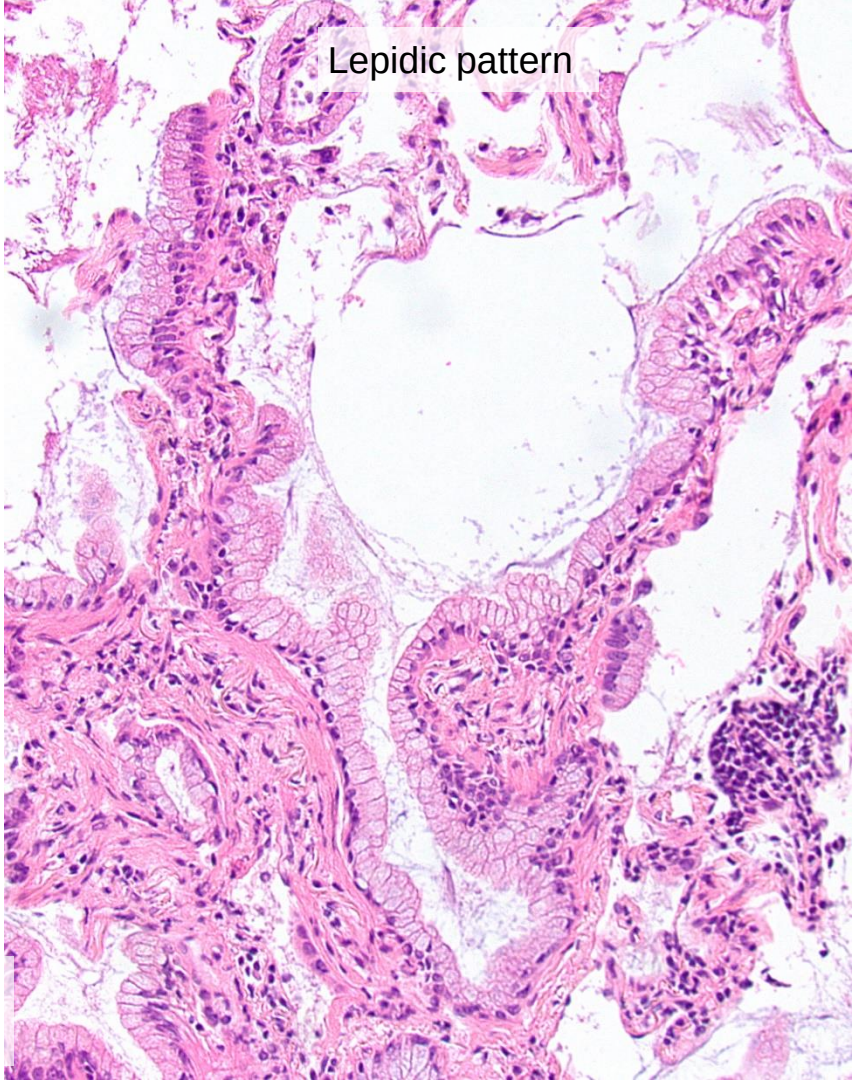
Small peripheral nodule often w/ or w/o surrounding grand-glass opacity

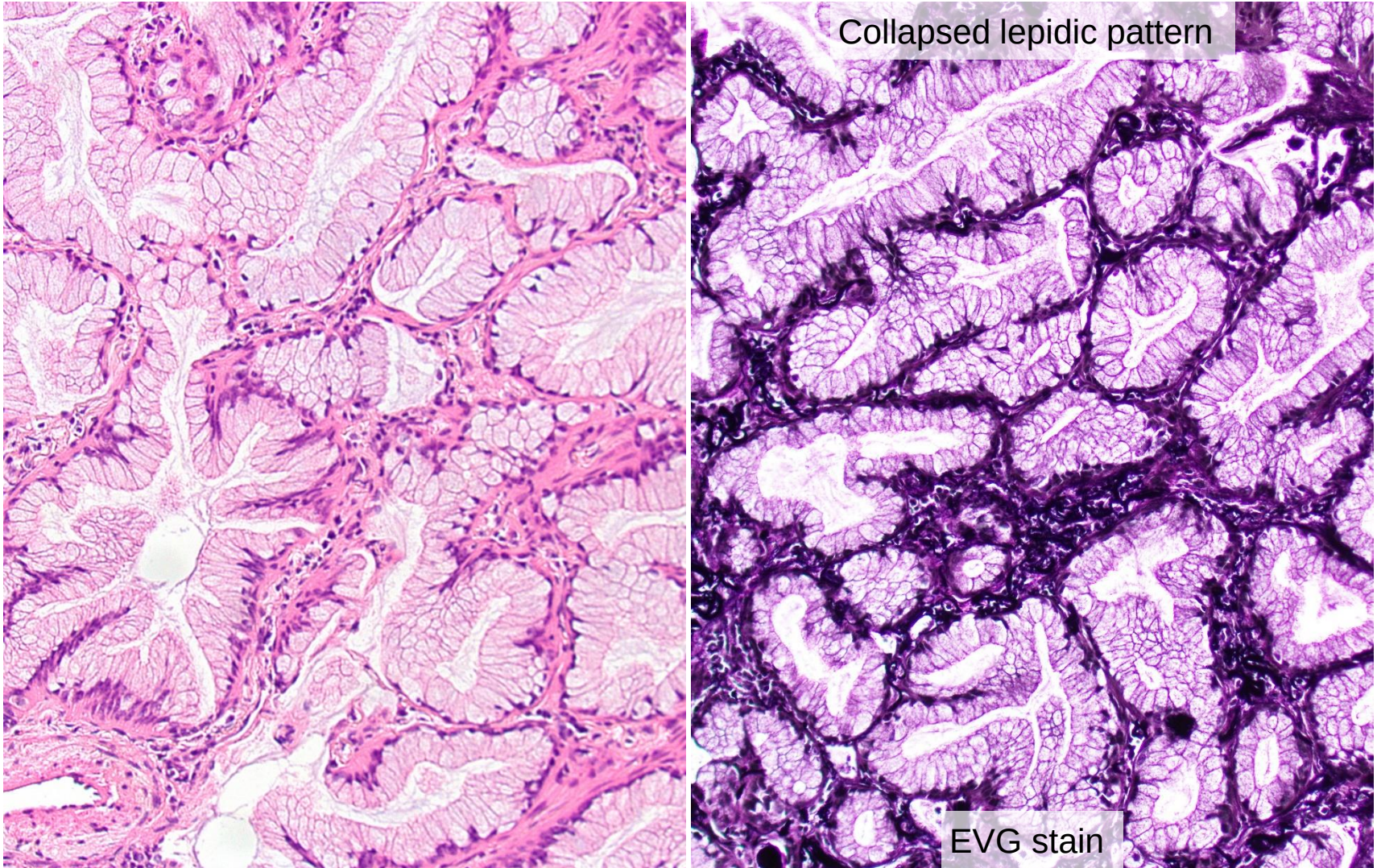


1.1 cm peripheral nodule



Well-formed glands composed of tall columnar cells w/ abundant mucin and basally located small nuclei

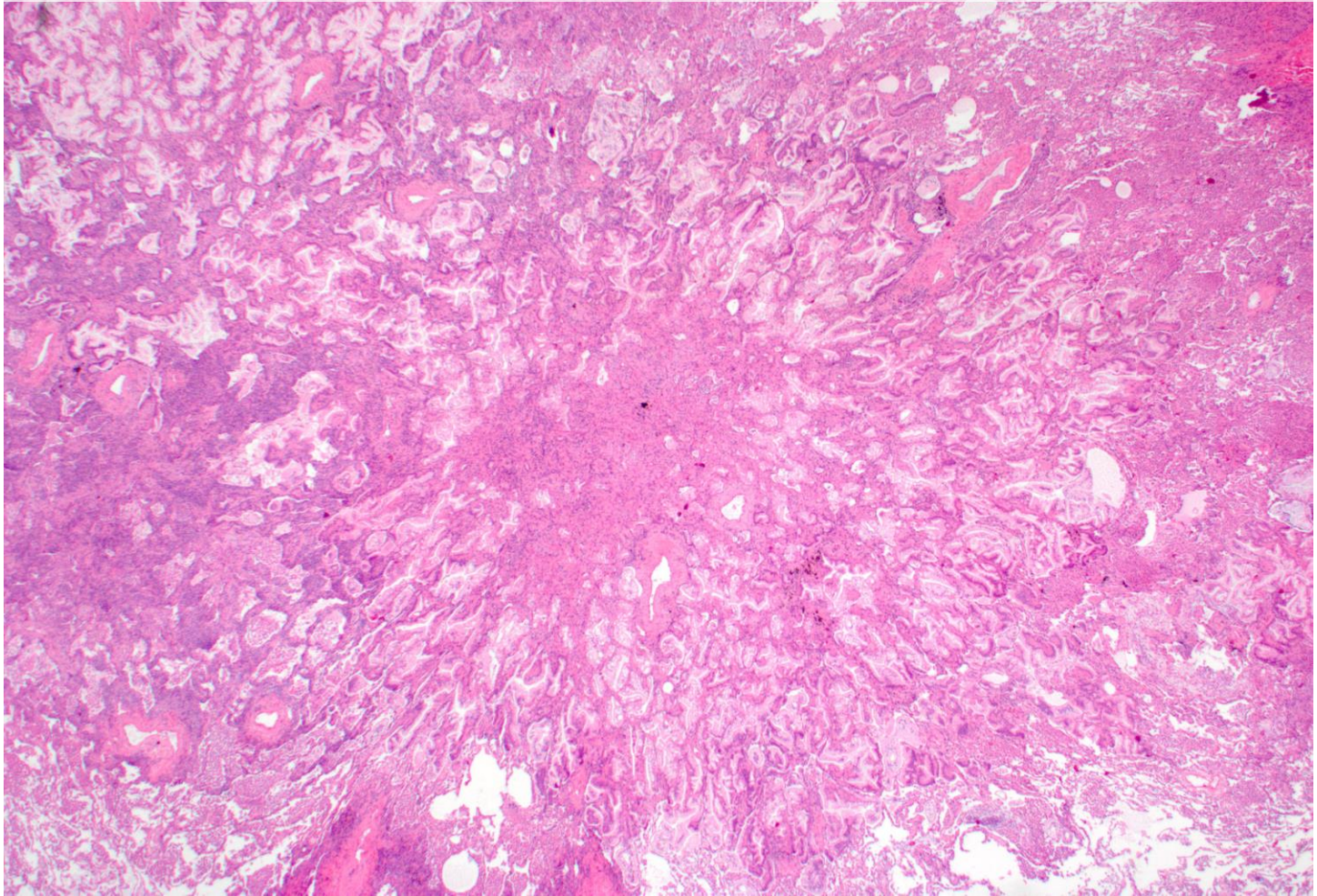


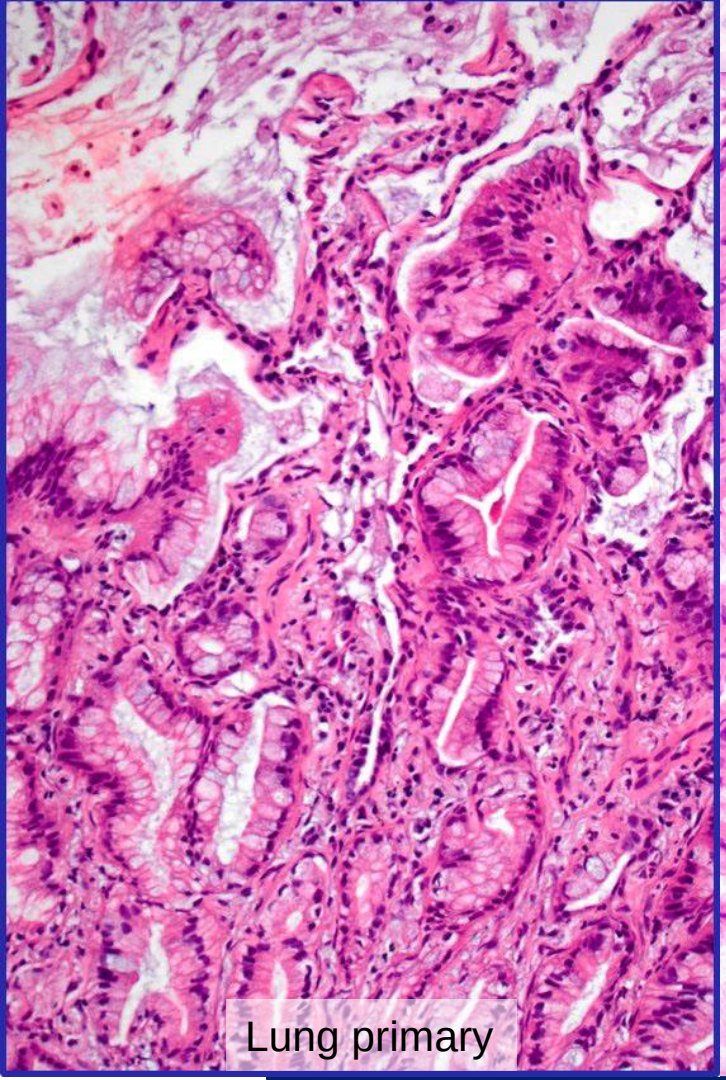

Collapsed lepidic pattern
EVG stain

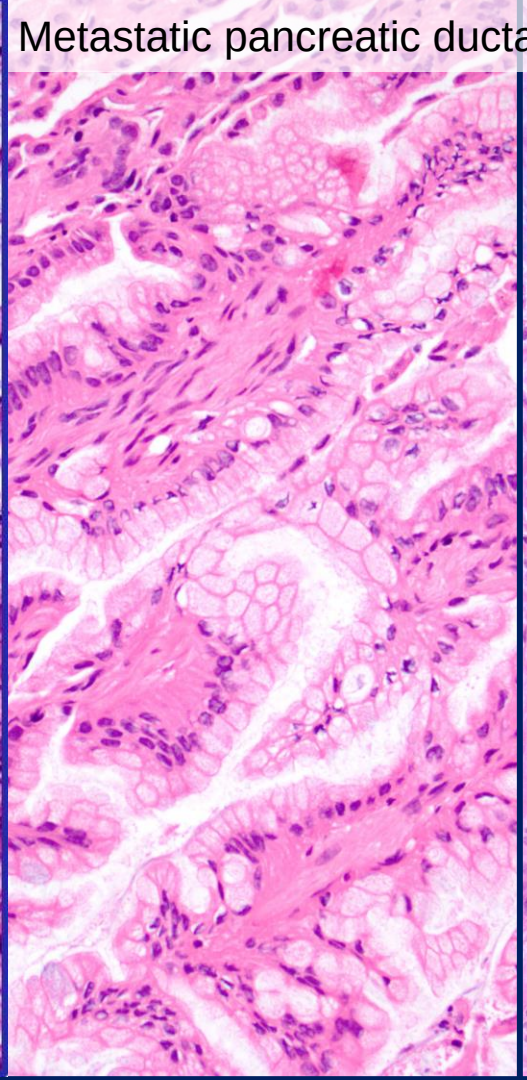
Differential Diagnosis

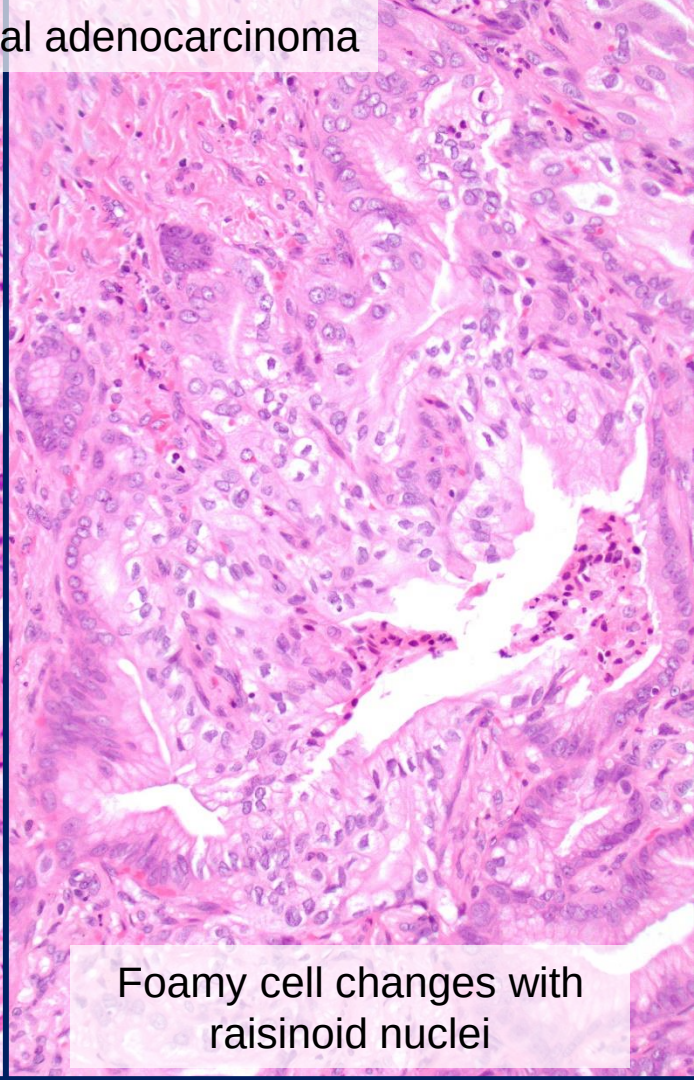
- Metastatic mucinous adenocarcinomas
  - Pancreas
  - Ovary
  - Breast
  - Colon & Rectum
- Conventional adenocarcinoma with mucin production
- Bronchiolar adenoma (proximal type)
- Peribronchiolar metaplasia with mucin
- Submucosal mucinous glands of bronchial tissue (on biopsy)

Example of pancreatic ductal adenocarcinoma met to the lung

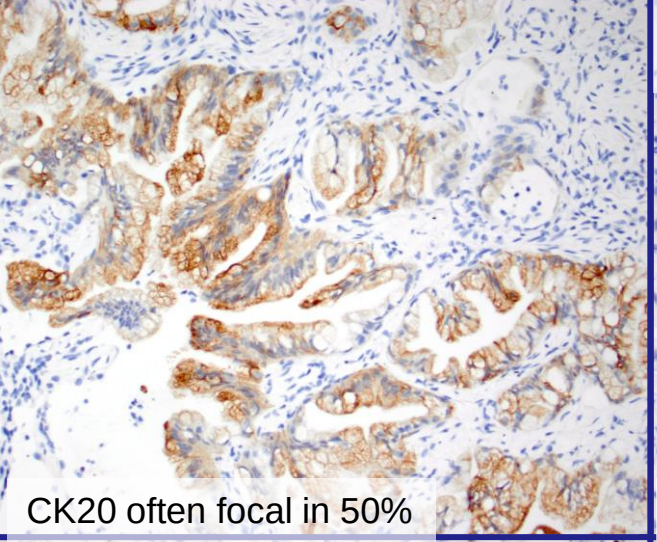


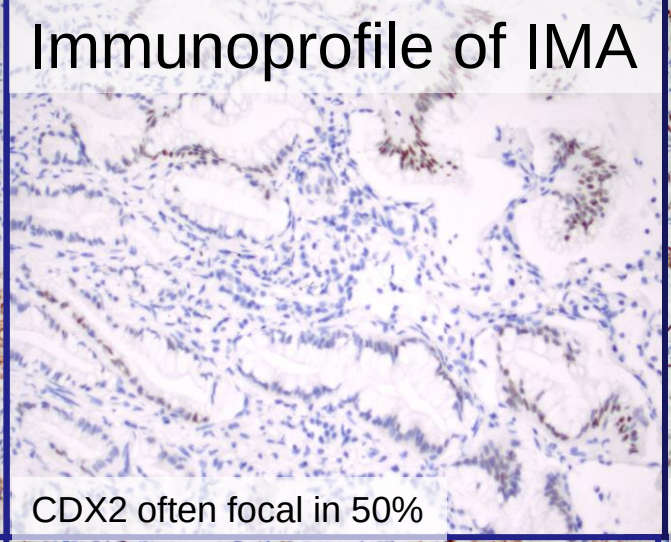

Lung primary

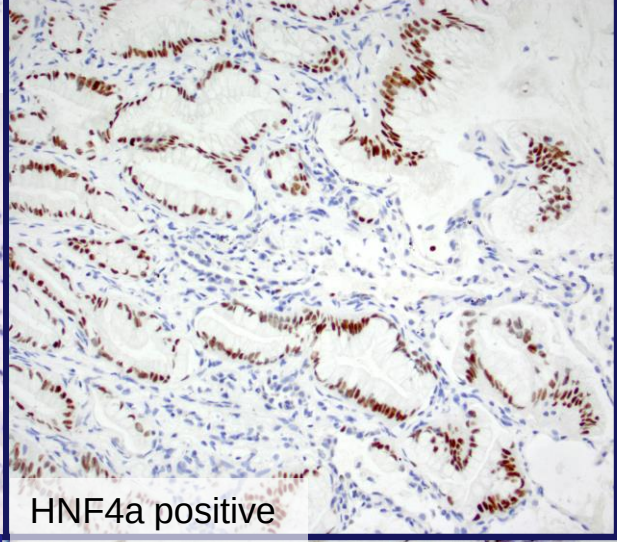

Metastatic pancreatic ductal adenocarcinoma

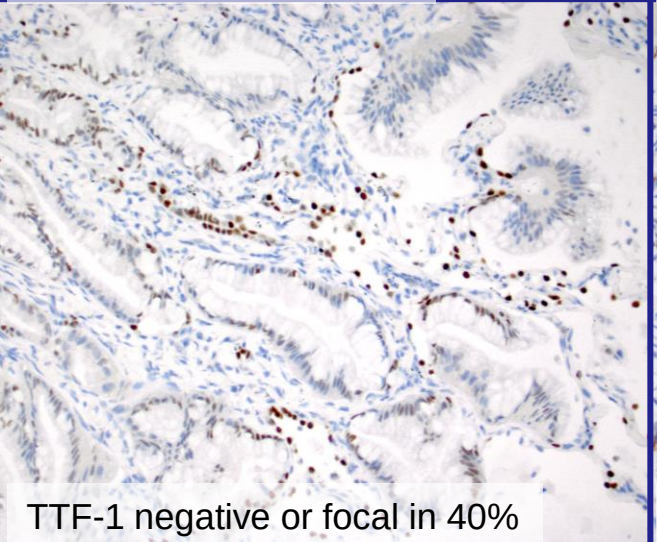

Foamy cell changes with raisinoid nuclei

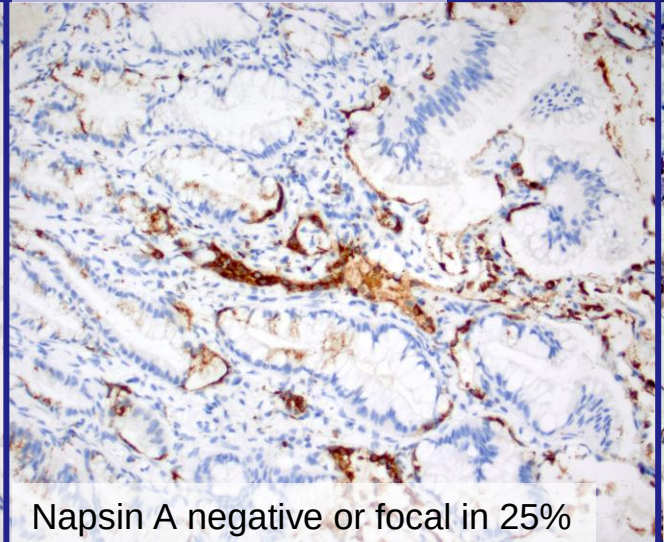
Immunoprofile of IMA

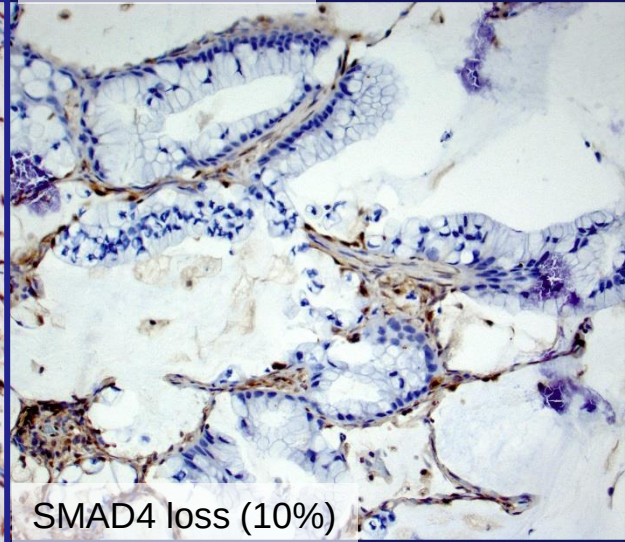

CK20 often focal in 50%


CDX2 often focal in 50%

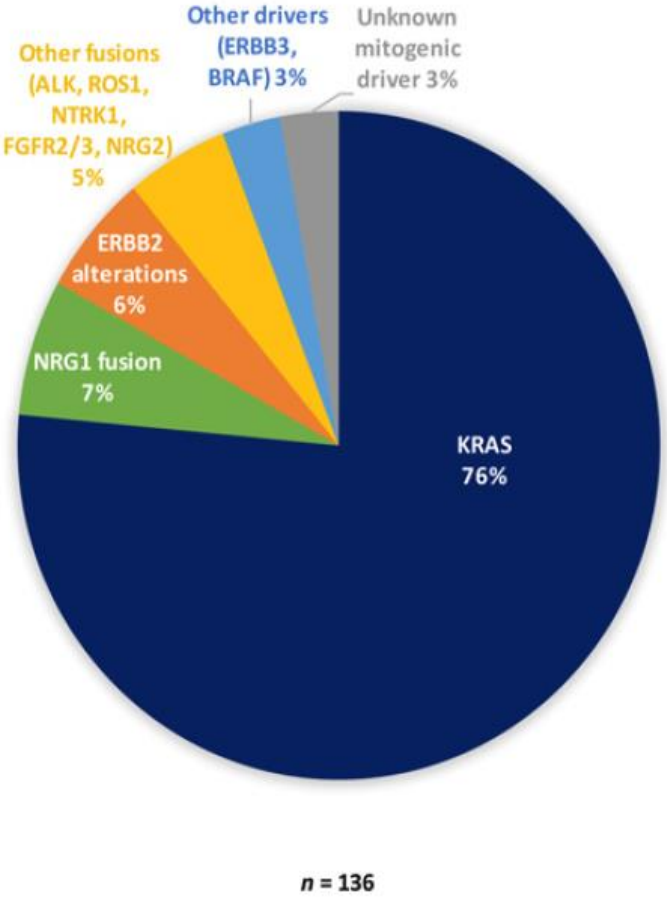

HNF4a positive

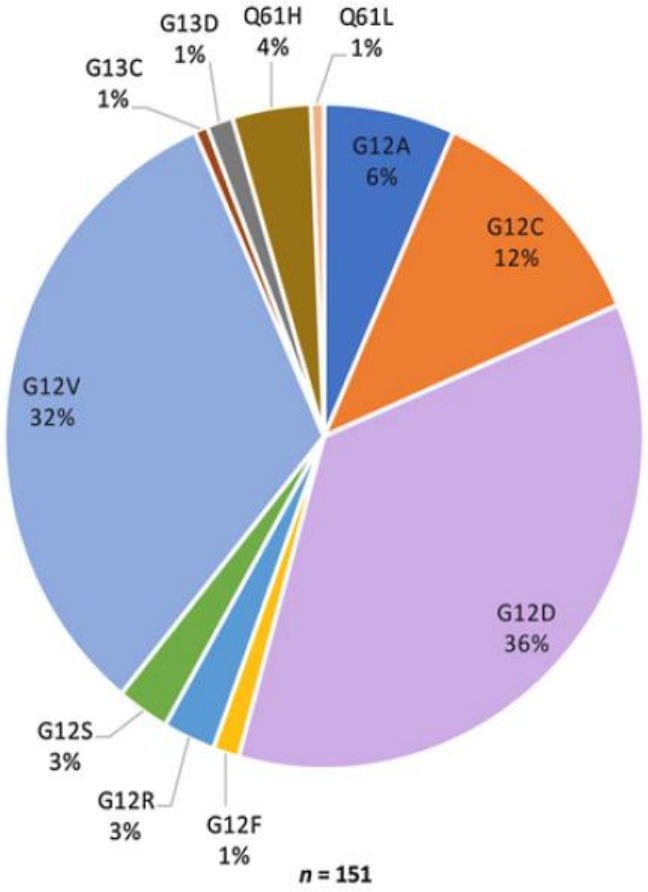

TTF-1 negative or focal in 40%


Napsin A negative or focal in 25%


SMAD4 loss (10%)

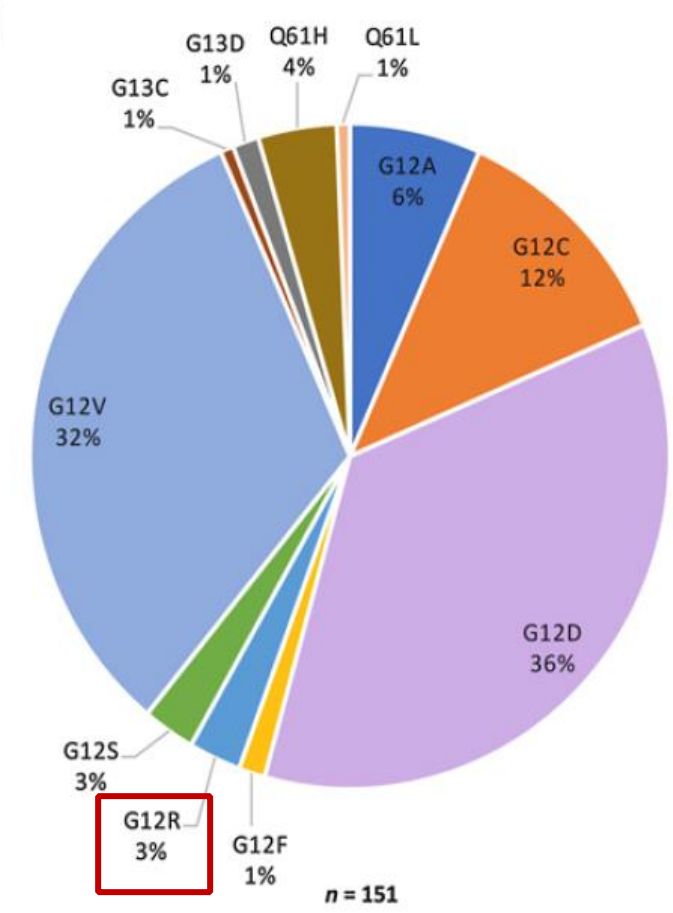
Molecular Profiles of IMA



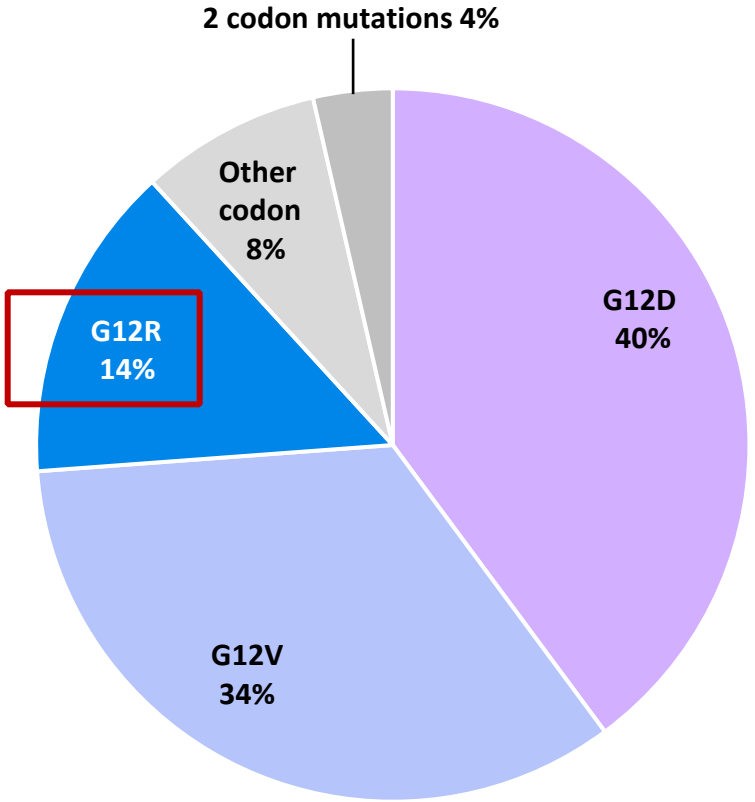


Chang JC, et al. Clin Cancer Res 2021;27:4066-76

KRAS Mutations in IMA

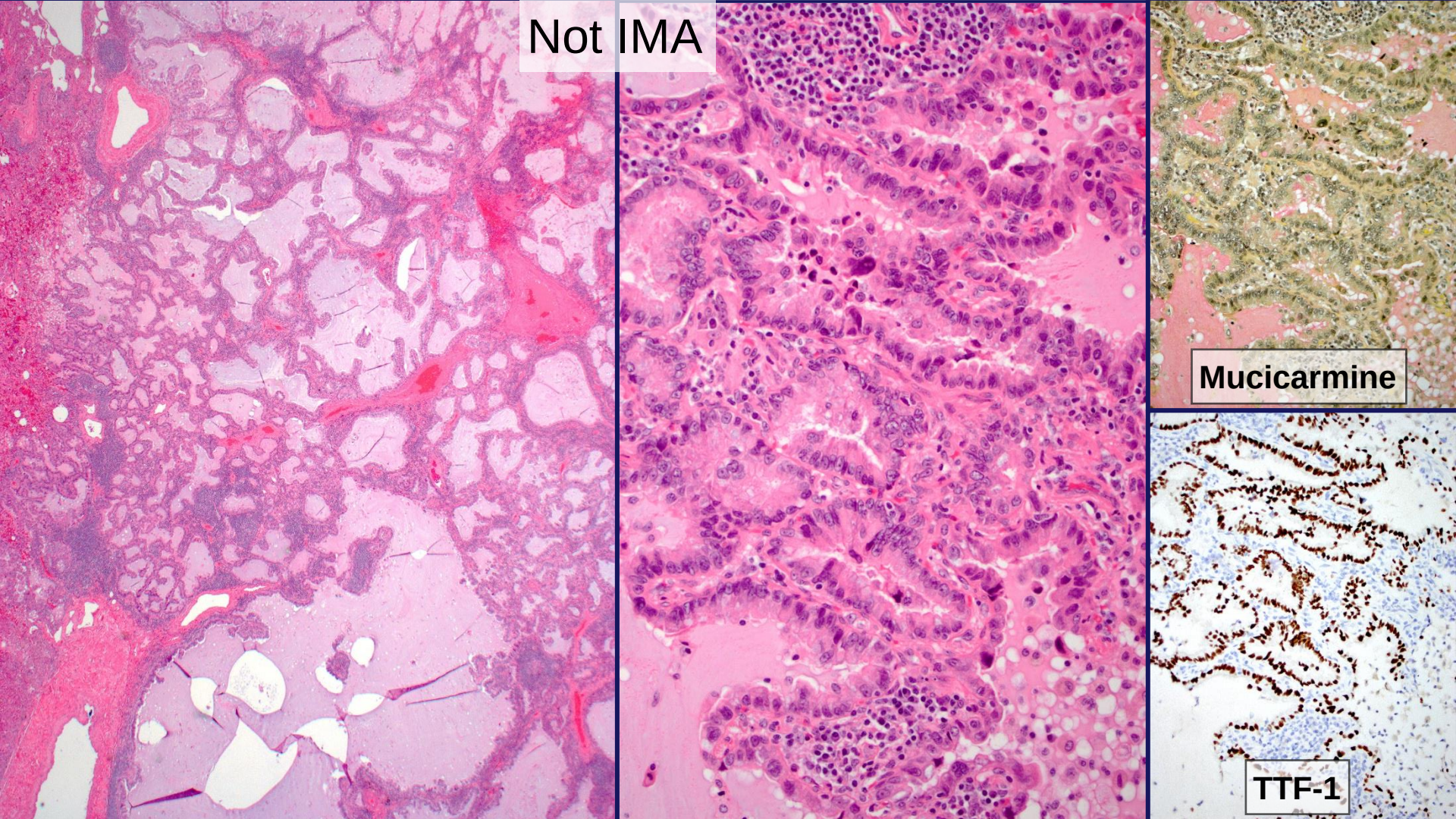


KRAS Mutations in PDAC

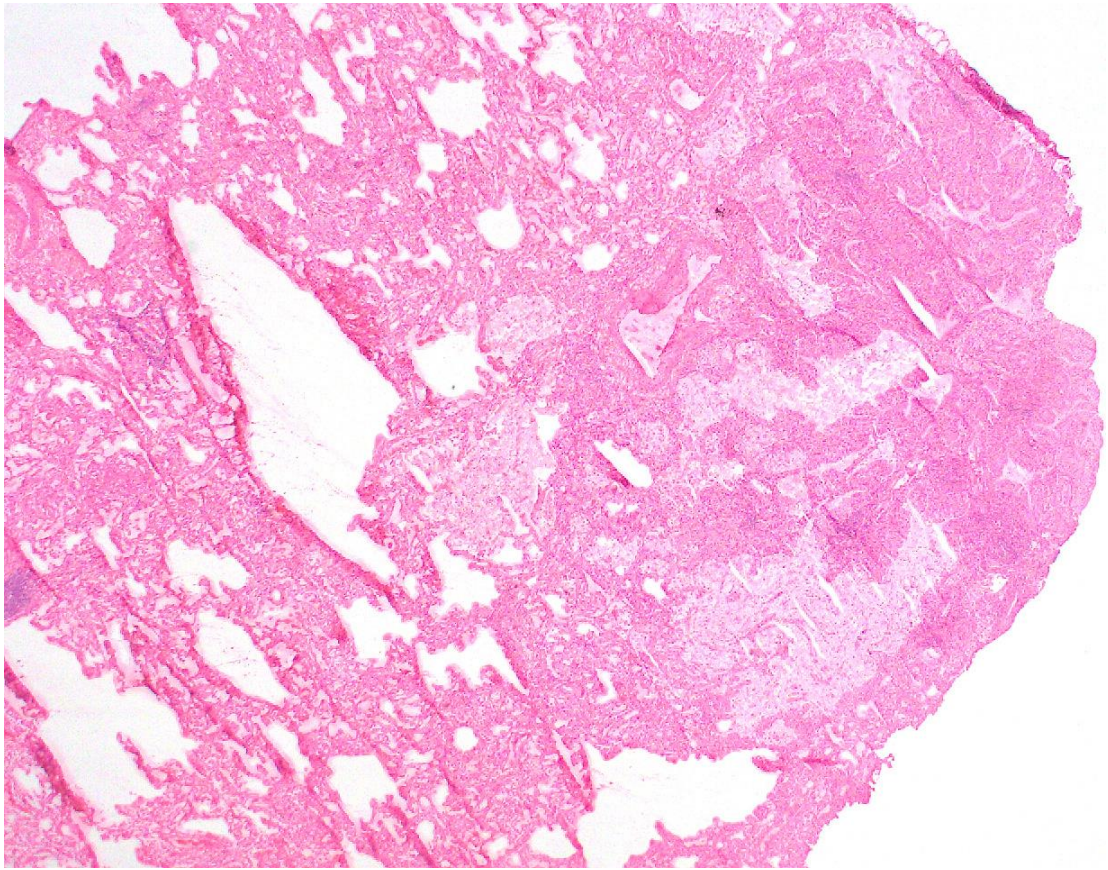


- *TP53* mutations are rare in IMA, while the majority of PDAC harbor *TP53* mutations

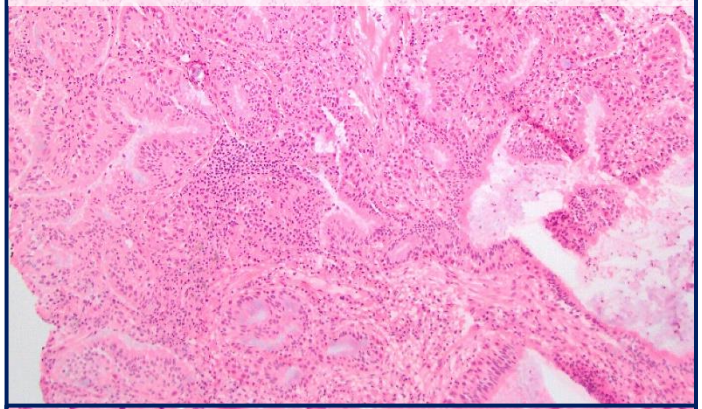
Chang JC, et al. Clin Cancer Res 2021;27:4066-76
Qian ZR, et al. JAMA Oncol 2018;4:e173420
Shim HS, et al. J Thorac Oncol 2015;10:1156-62

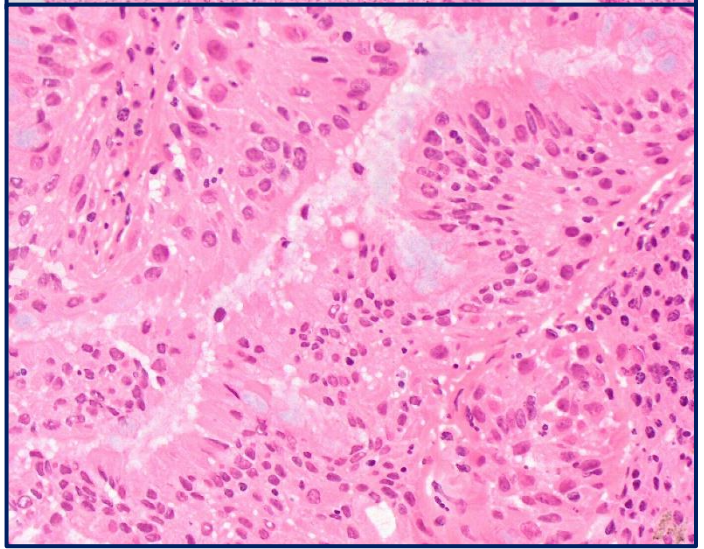

Not IMA
Mucicarmine
TTF-1

Intraoperative consultation for a 0.8cm lung nodule – FS residents thought that the lesion was c/w IMA

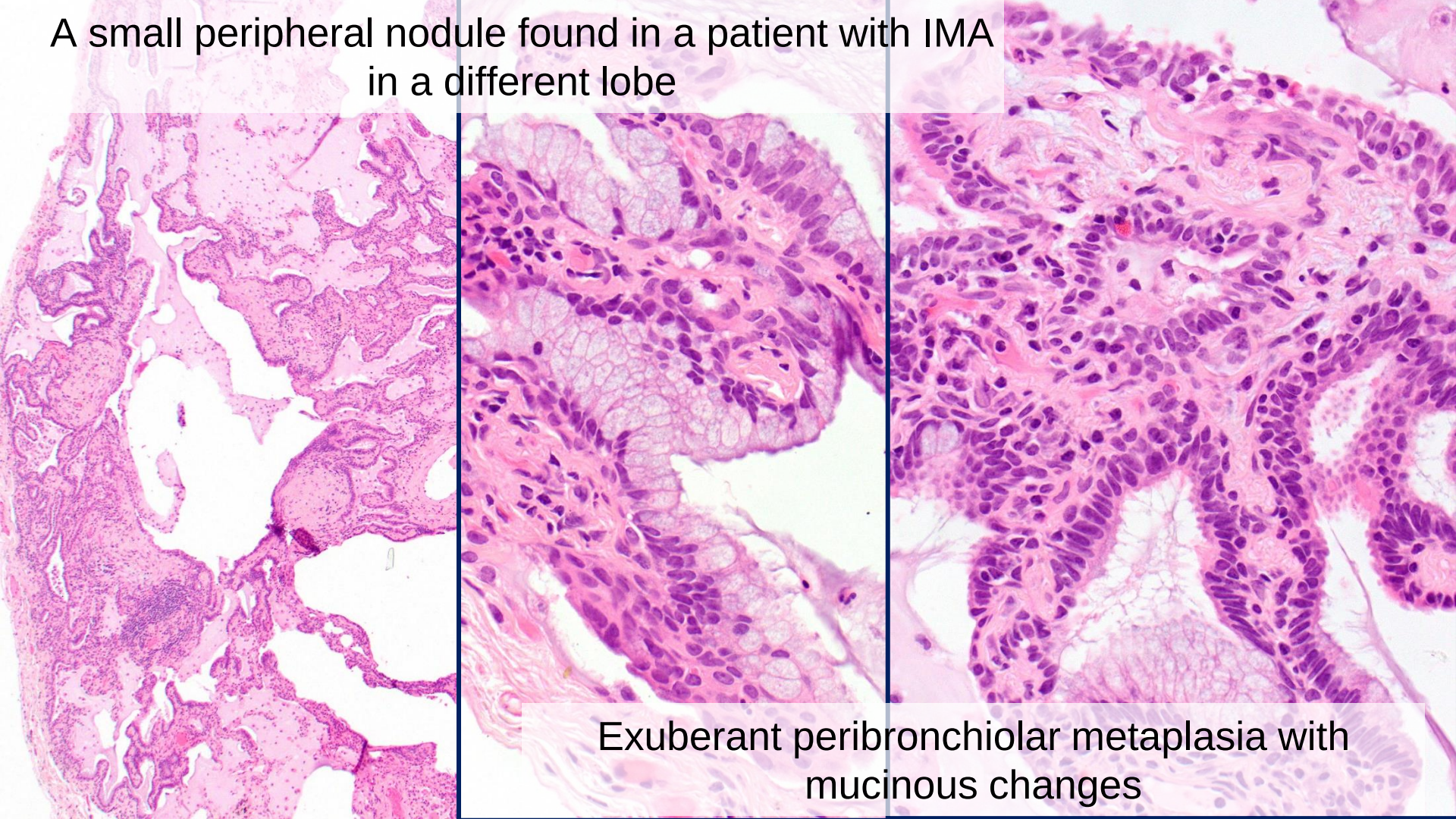


Bronchiolar adenoma / ciliated muconodular papillary tumor



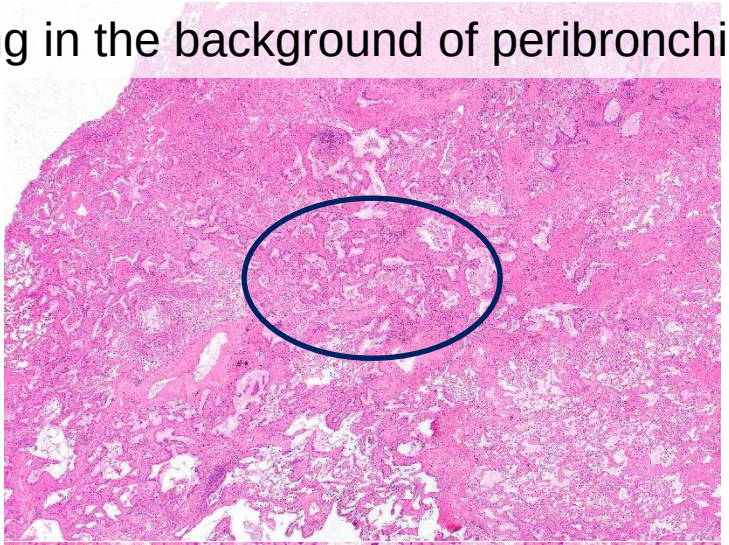


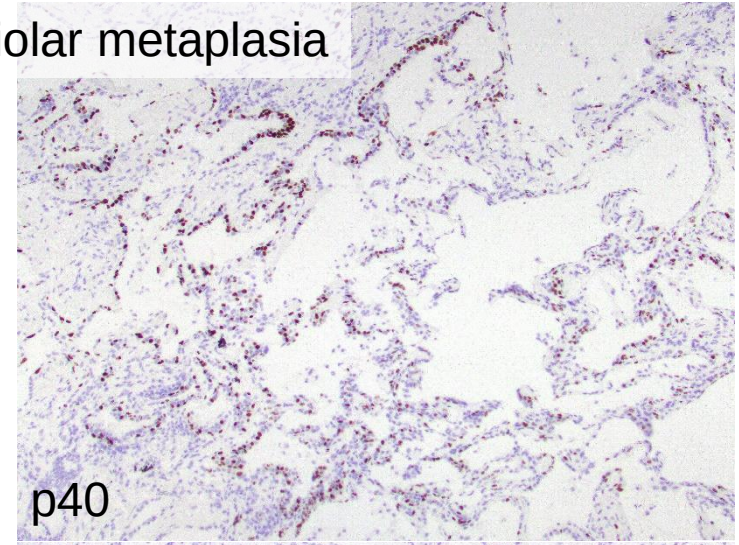
A small peripheral nodule found in a patient with IMA in a different lobe

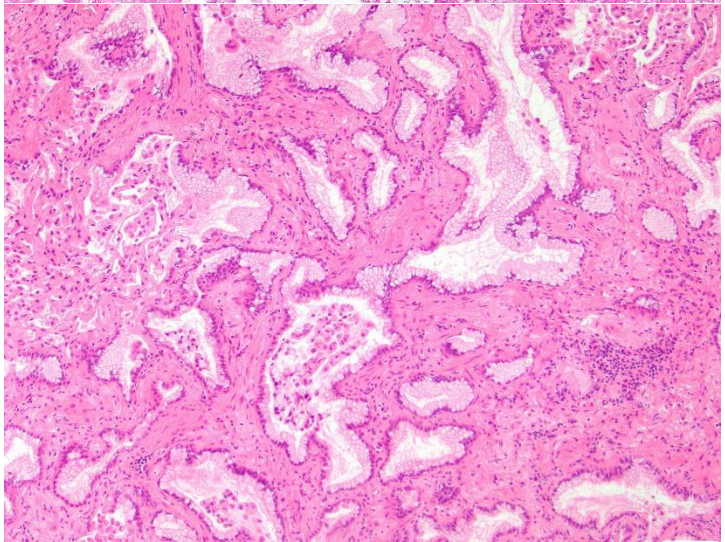


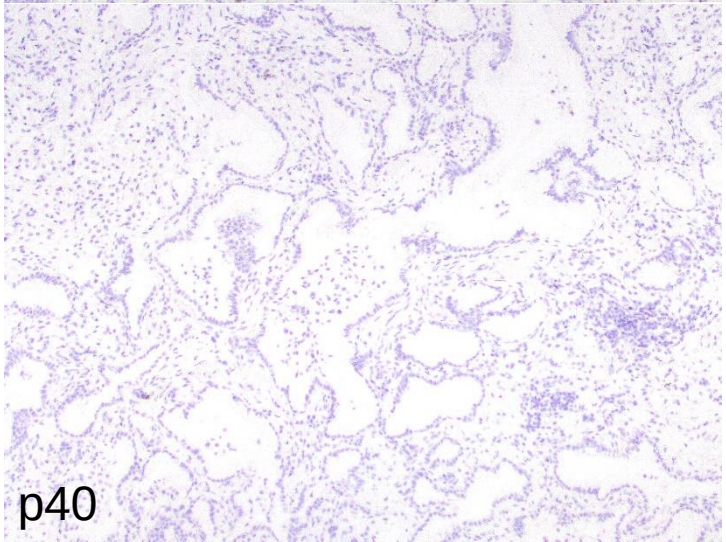
Exuberant peribronchiolar metaplasia with mucinous changes

IMA arising in the background of peribronchiolar metaplasia



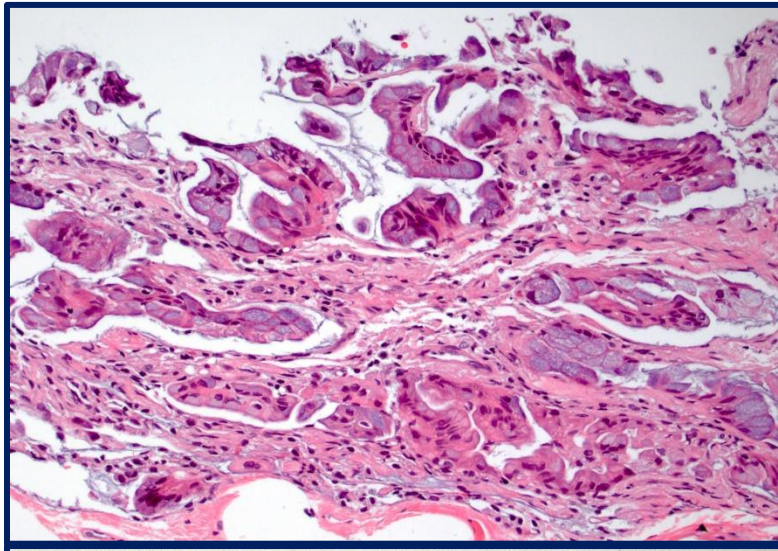


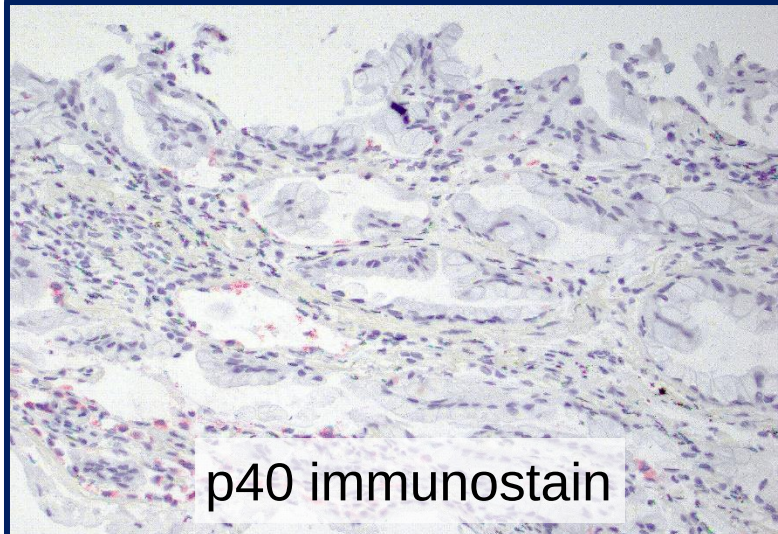




In small biopsies with predominant mucinous lepidic pattern

- Exclusion of mimickers (with p40 IHC to rule out the presence of basal layer, etc.)
- “Mucinous adenocarcinoma” terminology
- With a note about differential diagnoses including mucinous AIS, mucinous MIA, IMA, mixed mucinous and non-mucinous adenocarcinoma and non-mucinous adenocarcinoma w/ mucinous features





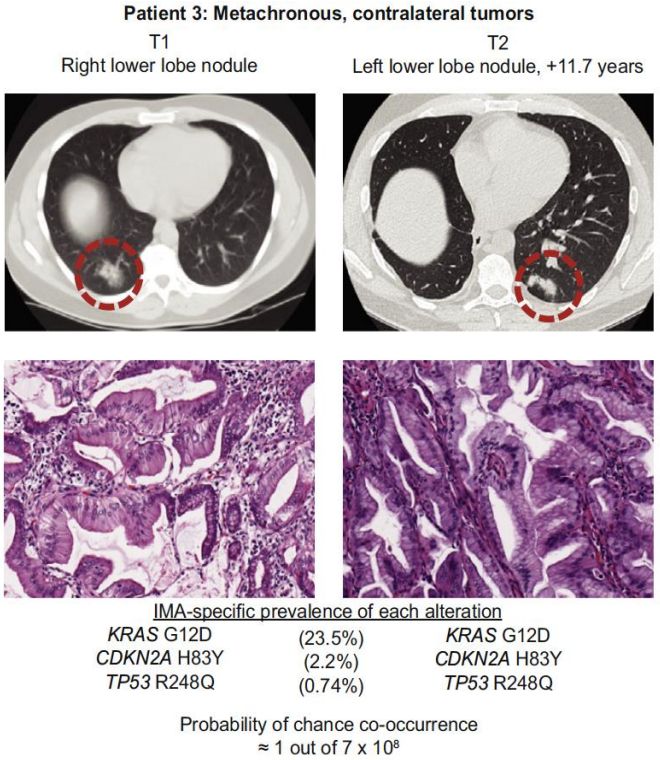
IMA – Prognosis

- Conflicting reports on prognosis of early stage tumors – worse, same and better than conventional adenocarcinomas – likely due to small numbers of resected cases
- Could recur in the contralateral lung after an extremely long latency (> 10 years)
- Overall survival appears to be significantly better in patients with stage IV IMA than in those with stage IV conventional adenocarcinoma, if not treated
- Patients with IMA typically do not benefit from chemotherapy

Yoshizawa A, et al. Modern Pathol 2011;24:653-64, Warth A, et al. J Clin Oncol 2012;30:1438-46, Tsuta K, et al. Lung Cancer 2013;81:371-6, Lee HY, et al. J Thorac Oncol 2016;11:1064-73, Cha YJ, et al. Lung Cancer 2016;102:82-8, Boland JM, et al. Hum Pathol 2018;71:8-19, Yang AR, et al. J Thorac Oncol 2021;16:1188-99

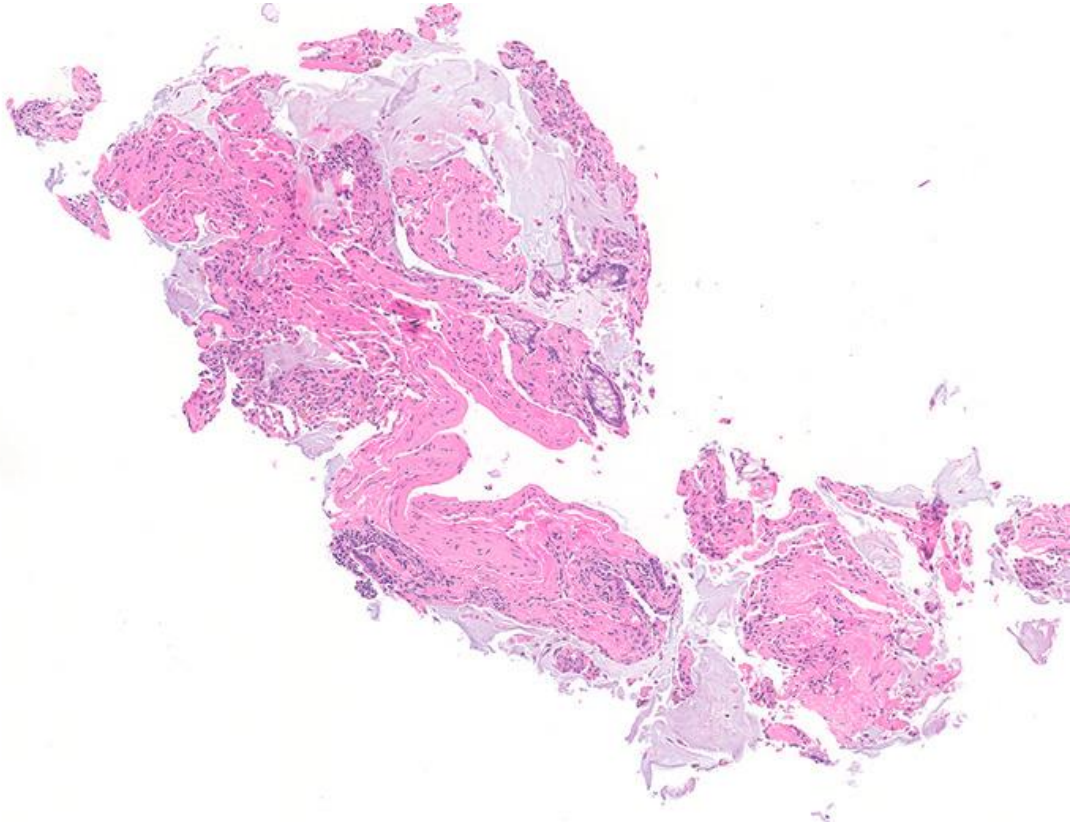
IMA with Spatially Separate Lung Lesions

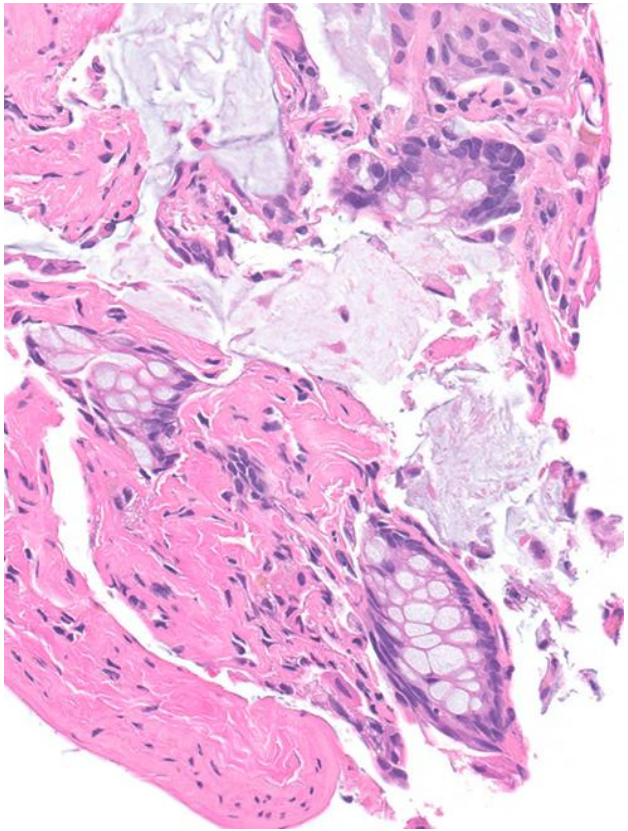
- Two separate IMAs in 24 patients
  - 11 synchronous, 13 metachronous
  - 19 contralateral, 5 ipsilateral
  - 18 with both nodules, 3 with both pneumonic infiltrates, 3 with mixed
- The two lesions are clonal in 23 of 24 by molecular profiling (with NGS used in 60%)
- Long latent (8.1 - 11.7 years) development of an isolated contralateral IMA in 4
- The presence of pneumonic infltrates was associated with poor outcome



Yang SR, et al. J Thorac Oncol 2021;16:1188-99

56-year-old woman with a 1.8 cm lung nodule

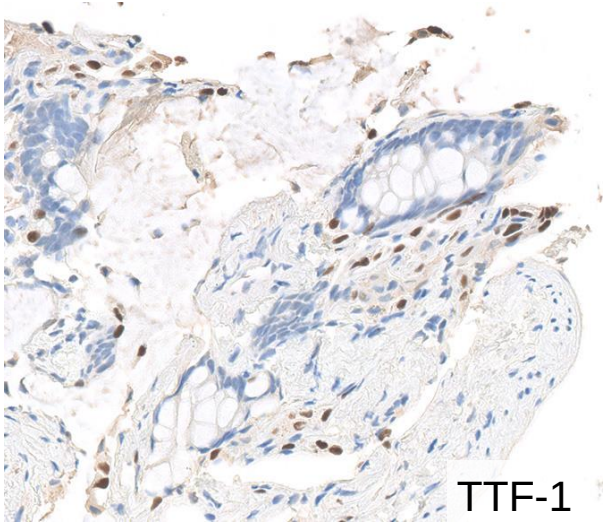


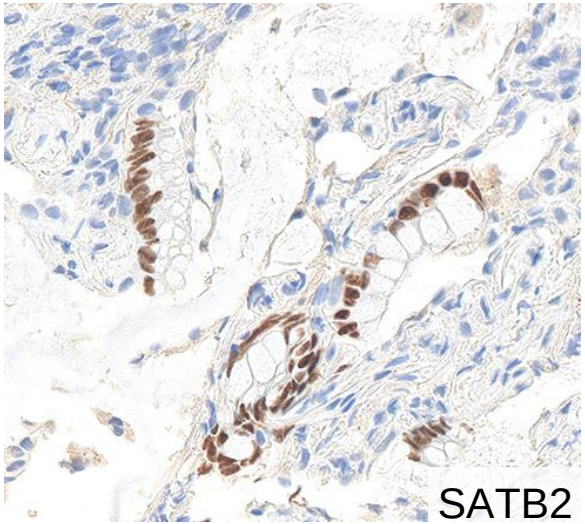


IHC Results

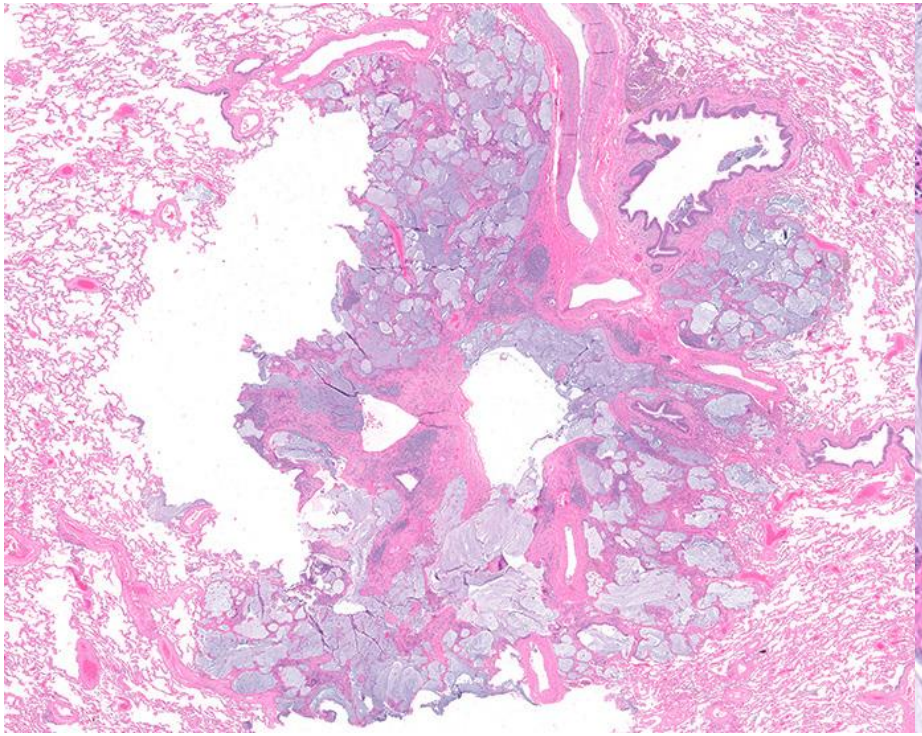
- CK20 +ve
- CDX2 +ve
- SATB2 +ve
- CK7 -ve
- TTF-1 -ve
- Napsin A -ve

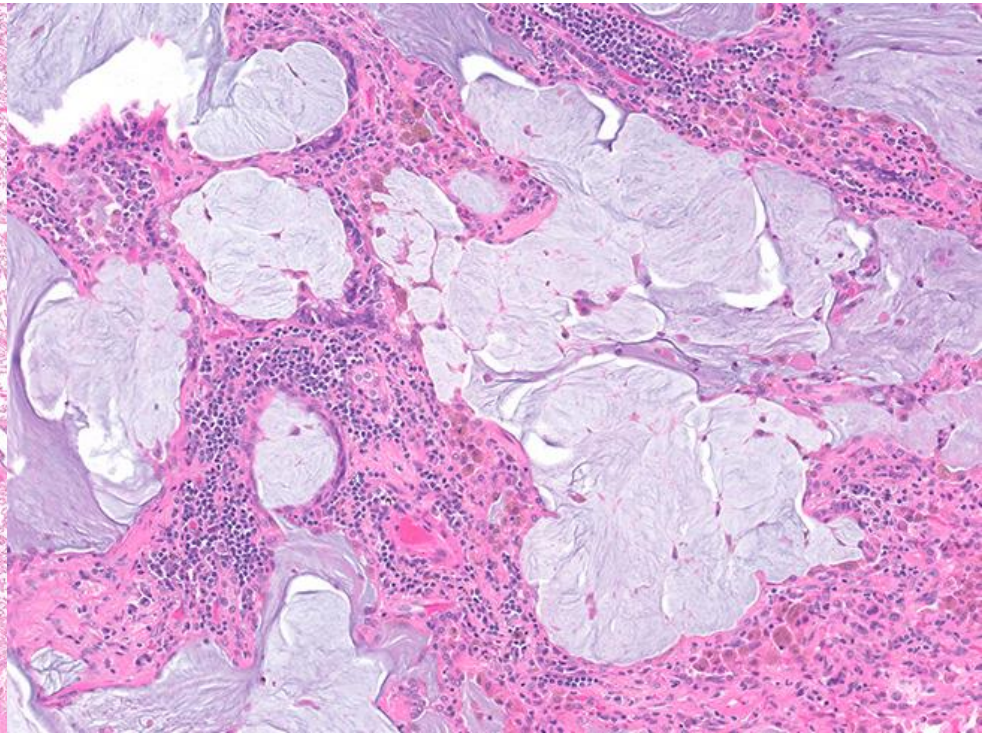
Lung primary vs. metastasis from lower intestinal or other primary?





Wedge Resection



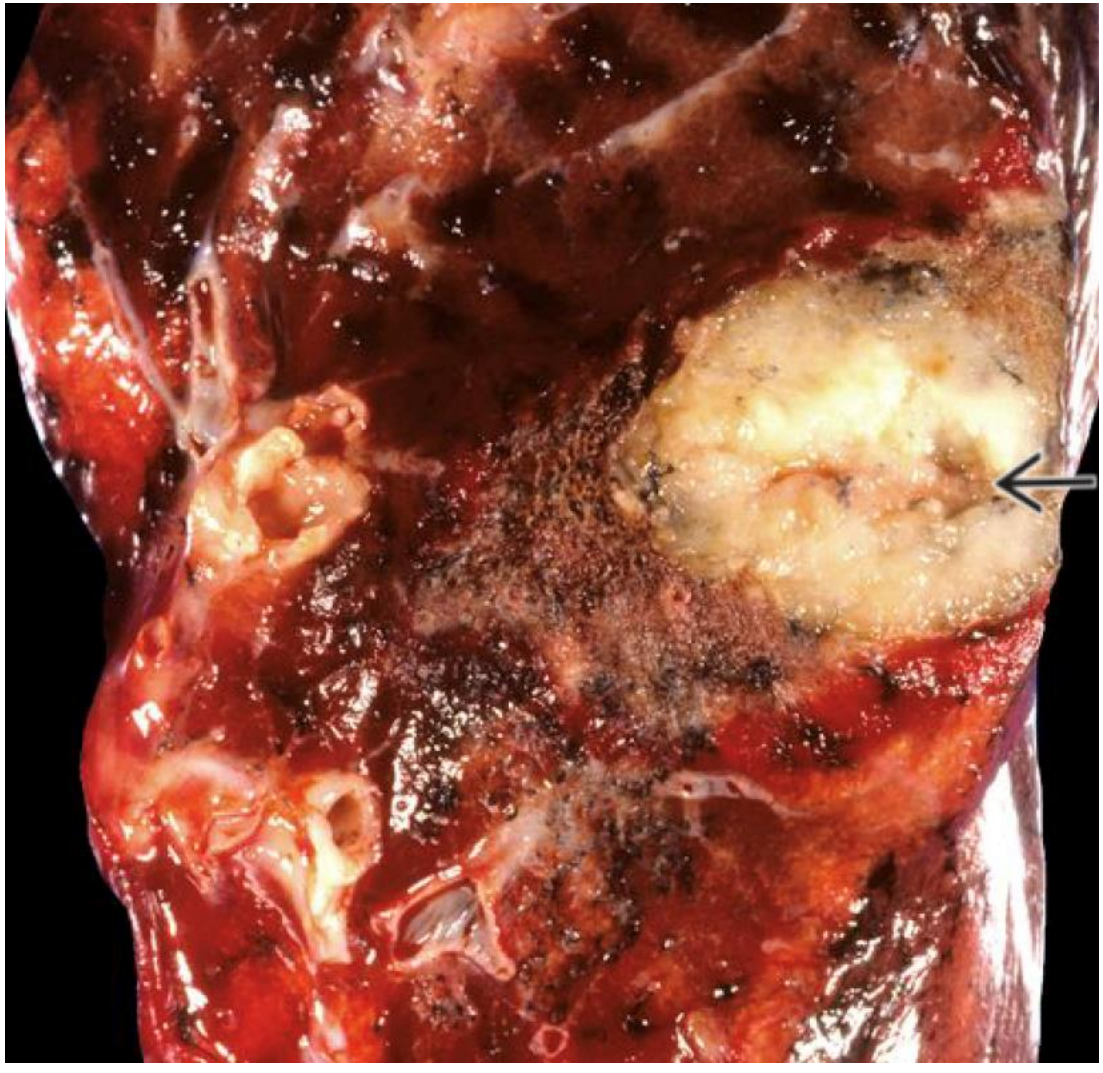


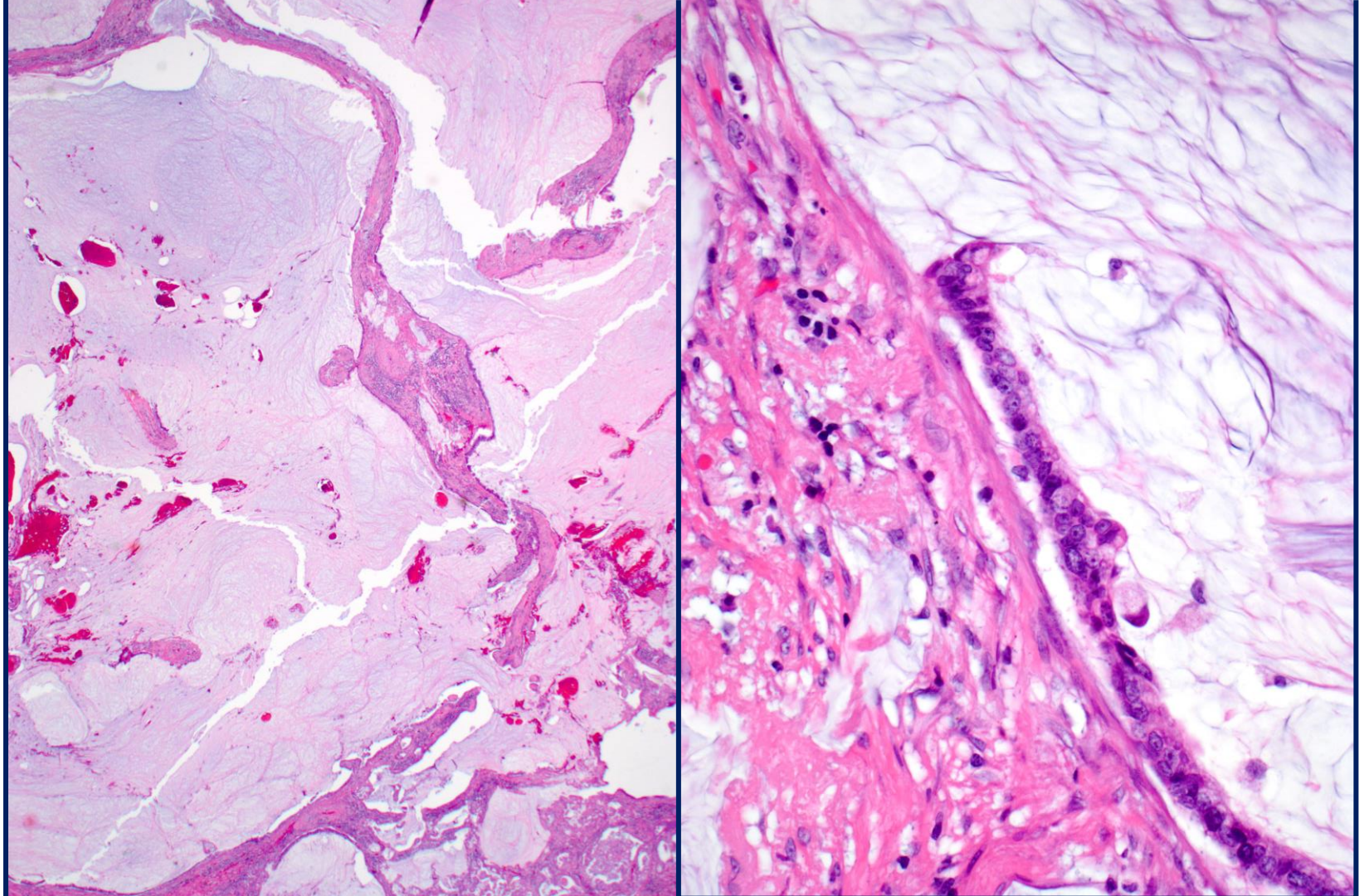
Further work-up revealed no other lesions
-> Colloid adenocarcinoma of the lung

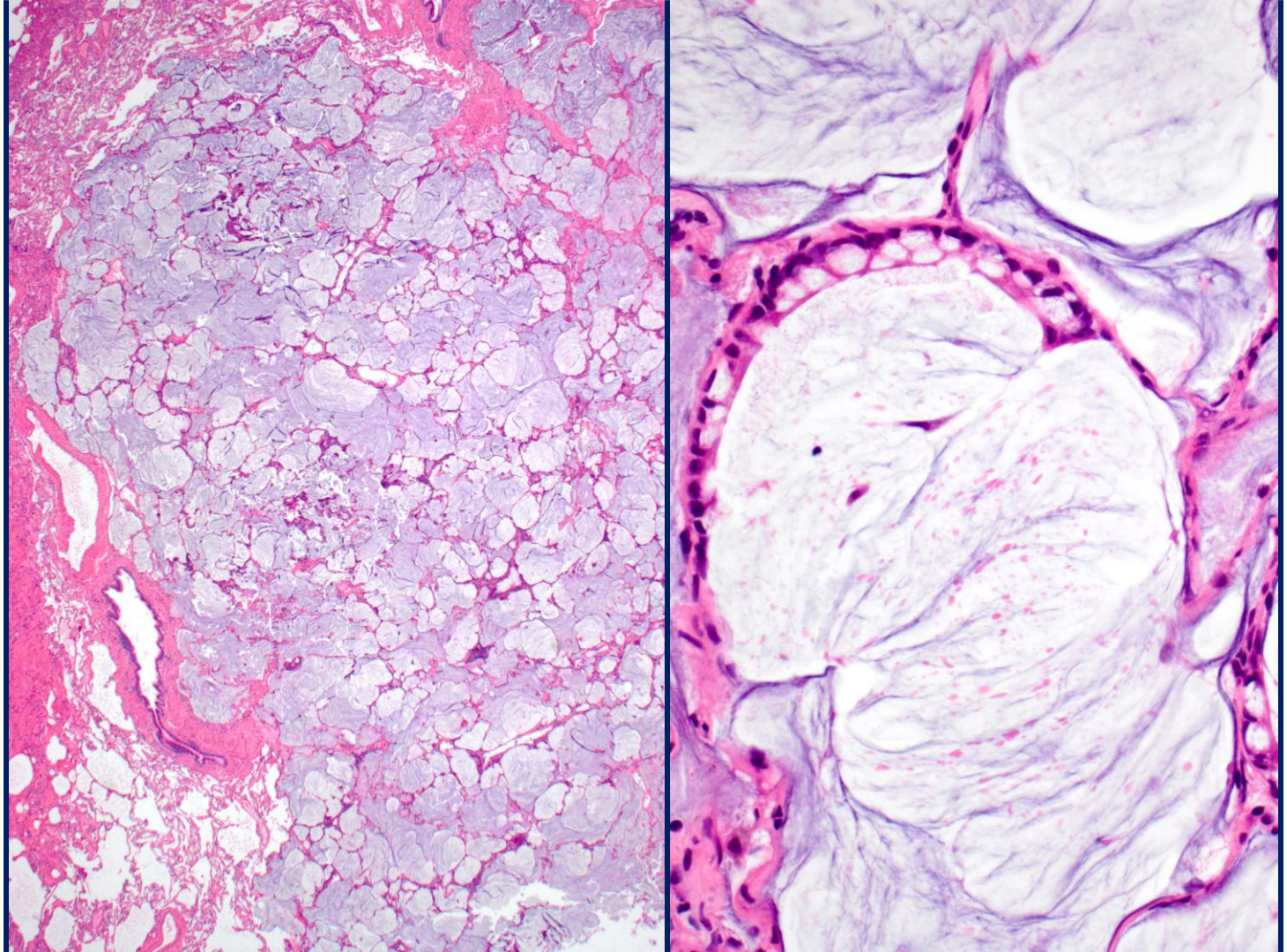
Colloid Adenocarcinoma

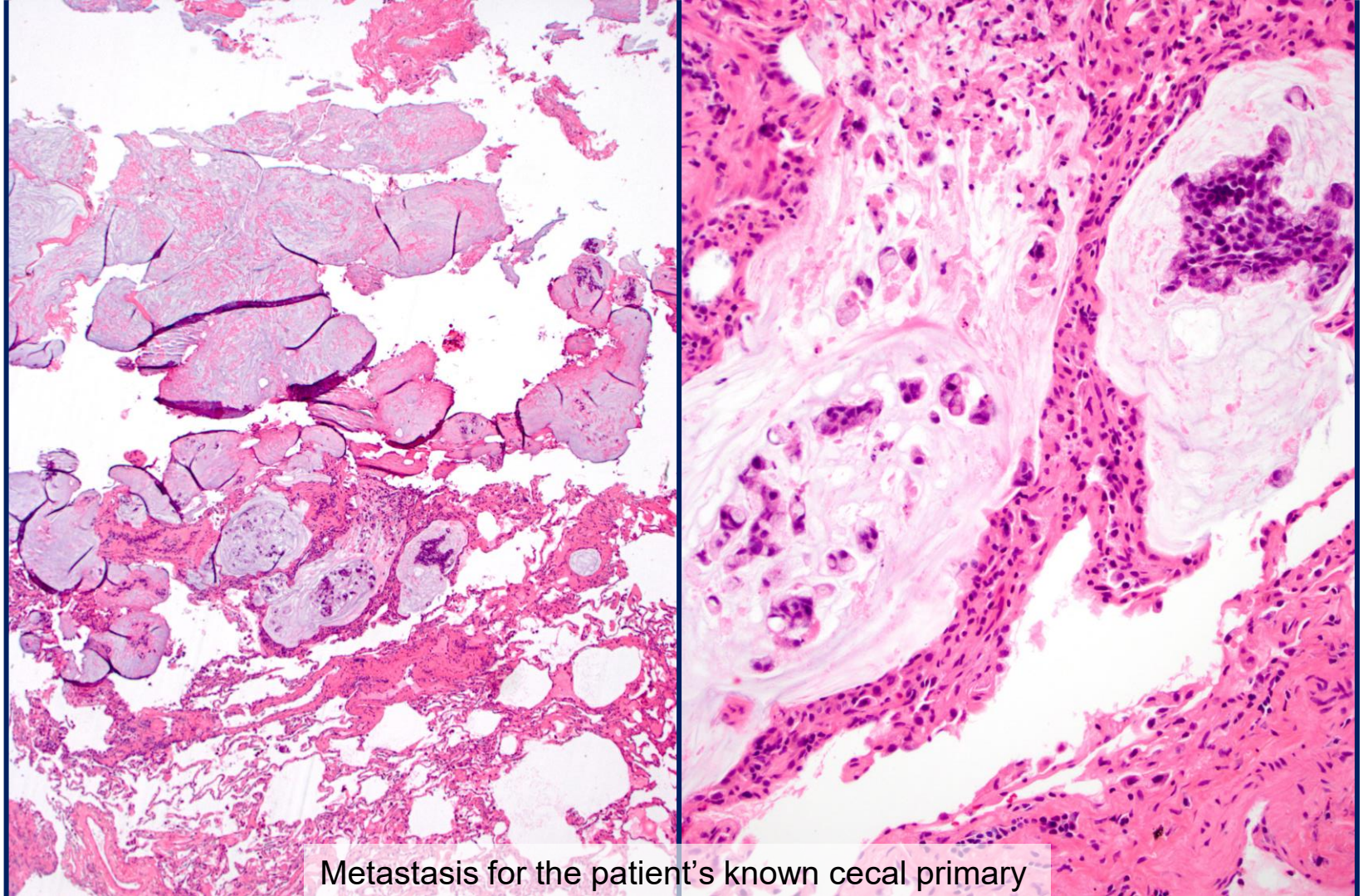
- Defined as an adenocarcinoma with abundant mucin pools distending alveolar spaces and destroying alveolar walls
- Colloid adenocarcinoma pattern in ≥ 50% of the tumor area warrants for the diagnosis, if mixed with other patterns of lung adenocarcinoma
- Previous terminology used for this entity: mucinous cystadenocarcinoma; mucinous cystic tumor of borderline malignancy
- *KRAS* mutations reported in 50% of these tumors
- Generally indolent clinical course (cumulative disease specific OS of approximately 80% at 5 year)

Rossi G, et al. Am J Surg Pathol 2004;28:442-52, Zenali MJ. et al. Human Pathol 2015;46:836-42, Jurmeister P, et al. Lung Cancer 2019;138:43-51



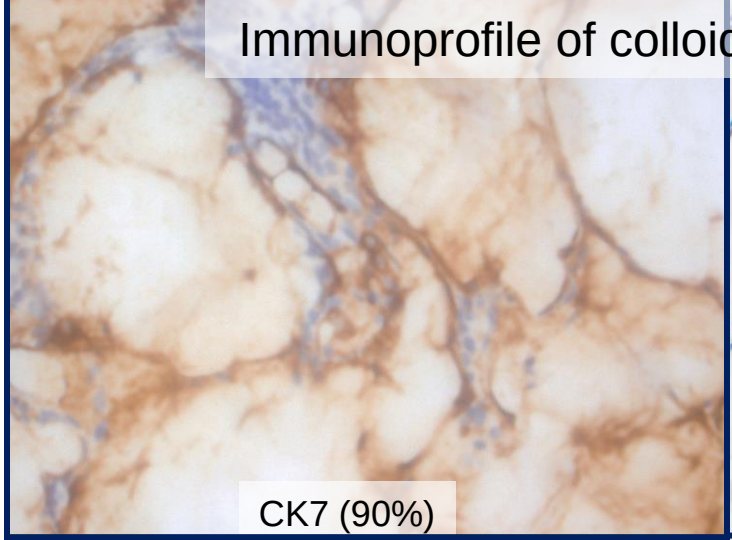




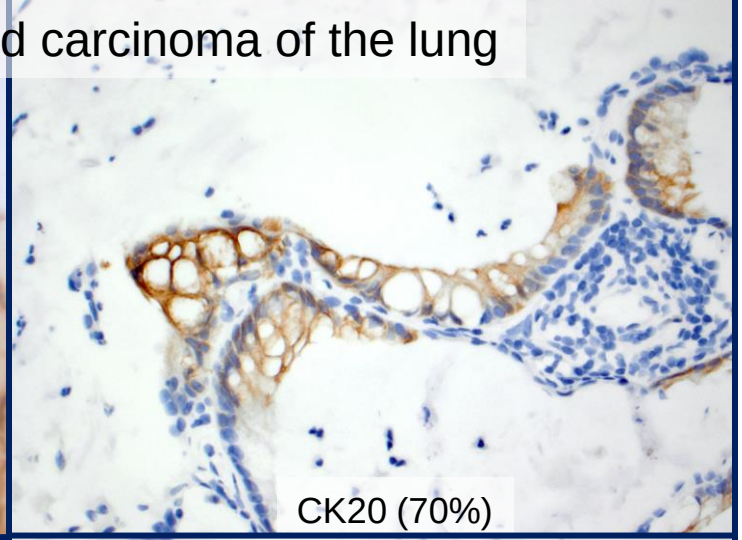


Metastasis for the patient’s known cecal primary

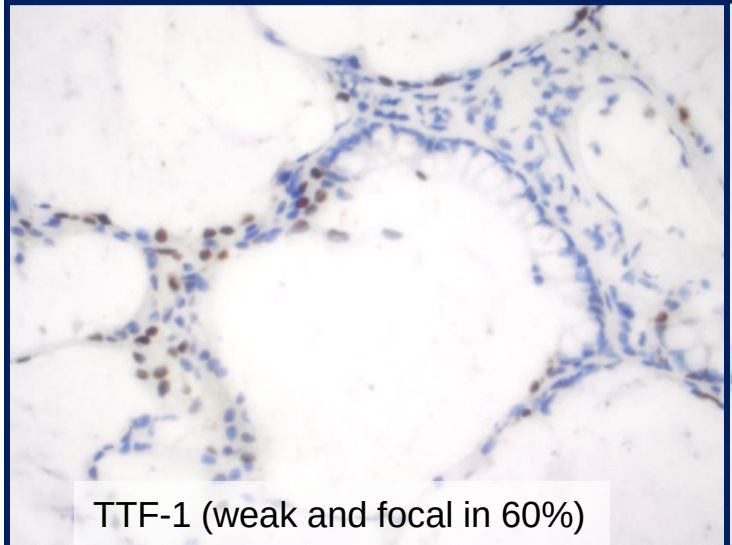
Immunoprofile of colloid carcinoma of the lung



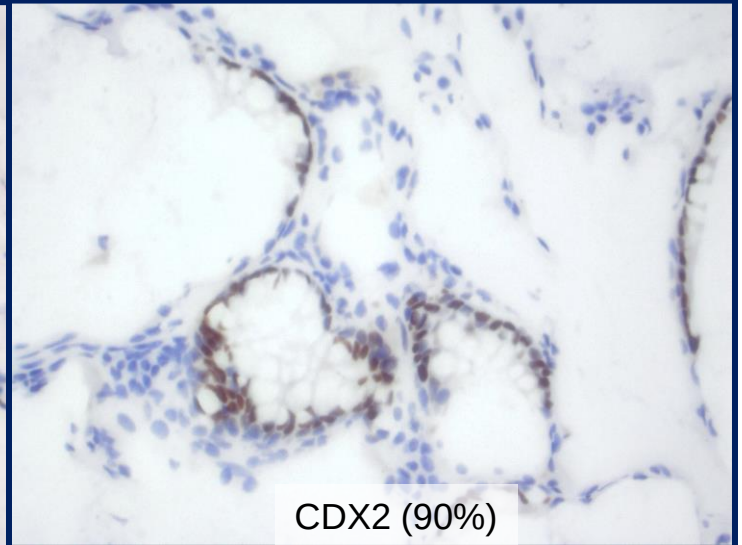
CK7 (90%)



CK20 (70%)



TTF-1 (weak and focal in 60%)



CDX2 (90%)

Immunoprofiles of Pulmonary Mucinous Adenocarcinomas and Their Mimickers

	TTF1	Napsin-A[a]	CK7	CK20	CDX2
Pulmonary adenocarcinomas					
Invasive mucinous adenocarcinoma[b]	-/+	-/+	++	+/-	+/-
Colloid adenocarcinoma	+/-	+/-	+	+/-	+
Signet ring cell carcinoma[c]	+	+/-	++	-	-
Solid adenocarcinoma with mucin	+	+/-	++	-	-
Mucinous adenocarcinoma	+/-	-/+	++	-/+	-/+
Upper GI tract[c]	-	-	+	+/-	+/-
Pancreas	-	-	++	+/-	+/-
Breast, mucinous	-	-	++	-	-
Ovary, mucinous	-	-	++	+/-	+/-

-: <10% of the examined tumor cells with positive expression

-/+: 10% - 40% positive

+/-: 40% - 70% positive

+: 70% - 90% positive

++: >90% positive

Clinicopathologic correlation is extremely important to differentiate between a mucin-producing lung primary and metastasis from an upper GI, pancreatobiliary, breast or ovarian primary

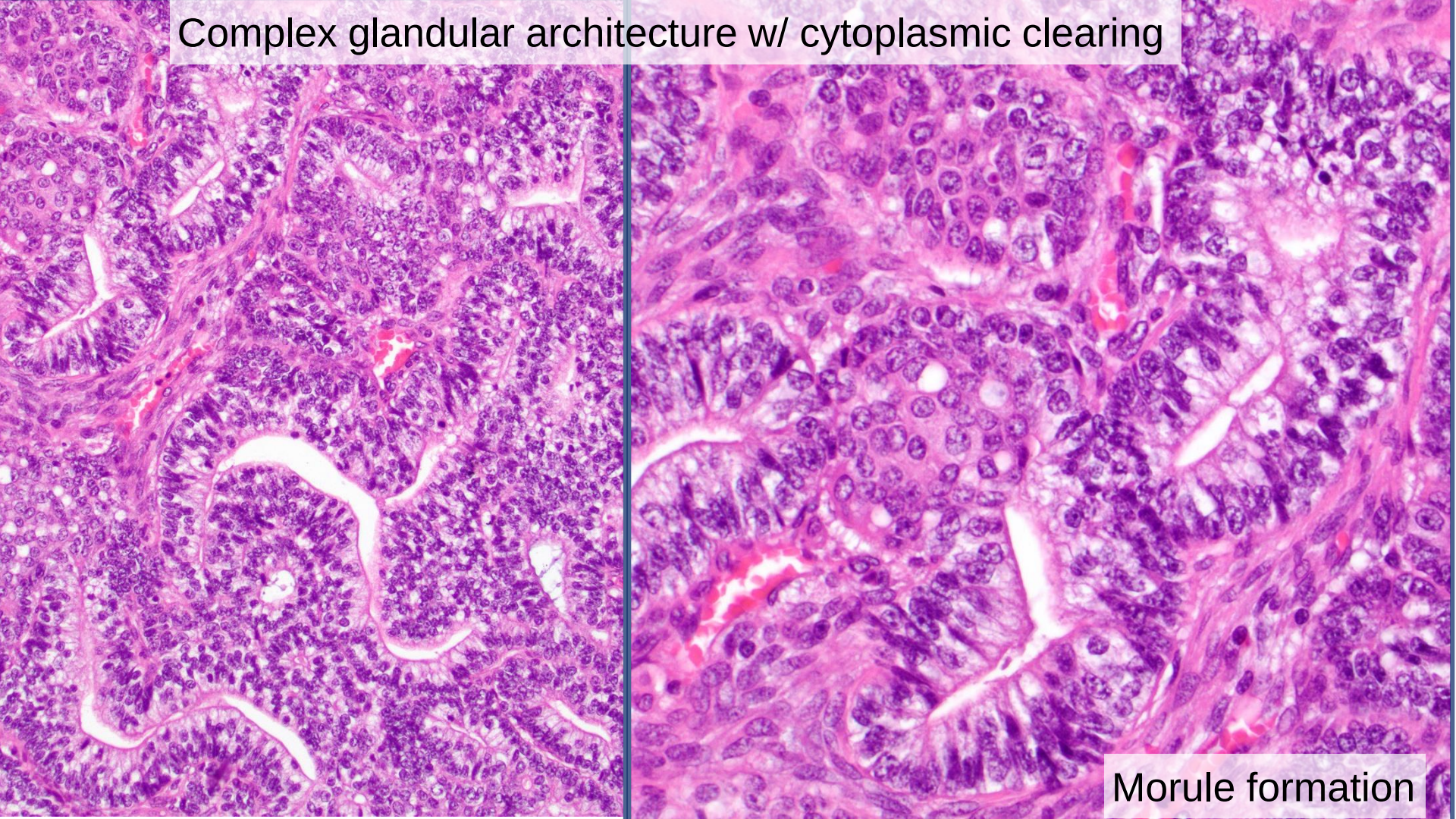
Yatabe Y, et al. J Thorac Oncol 2019;14:377-407

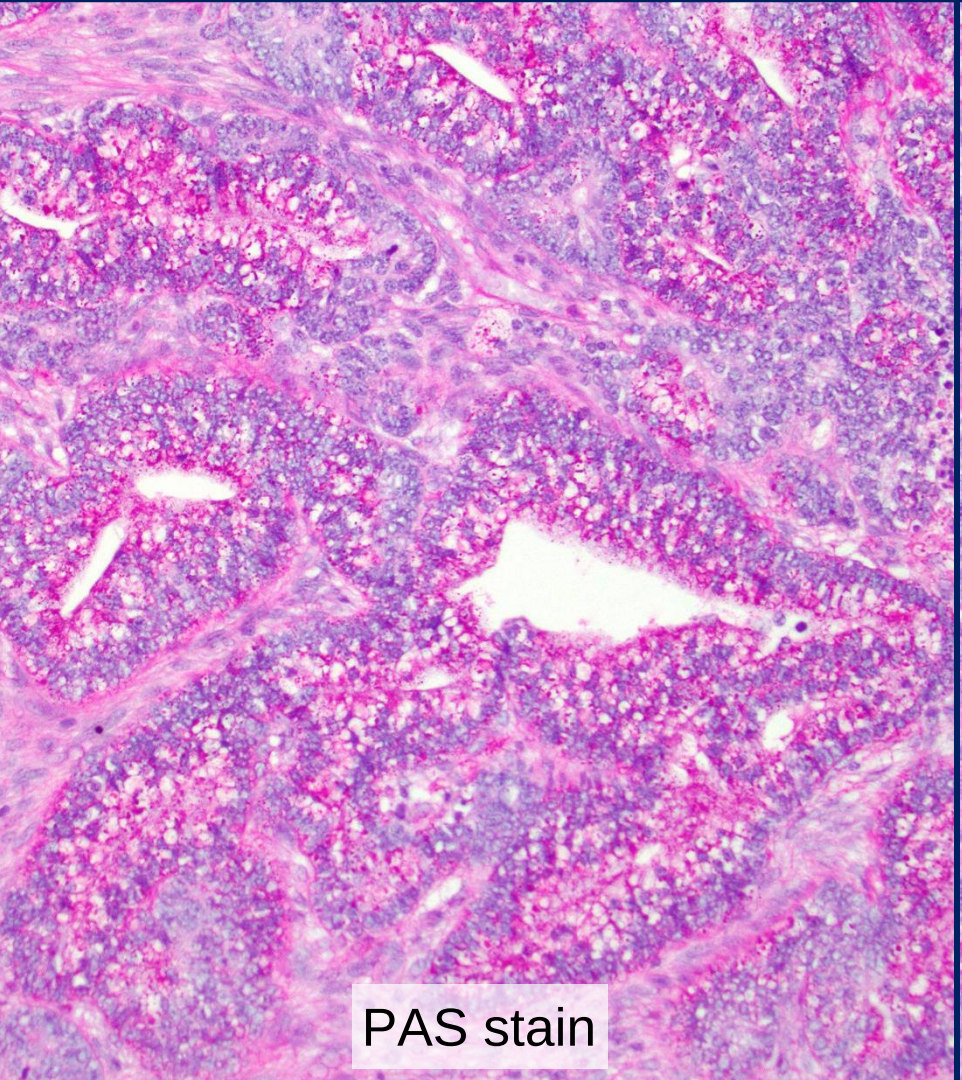
Fetal Adenocarcinoma

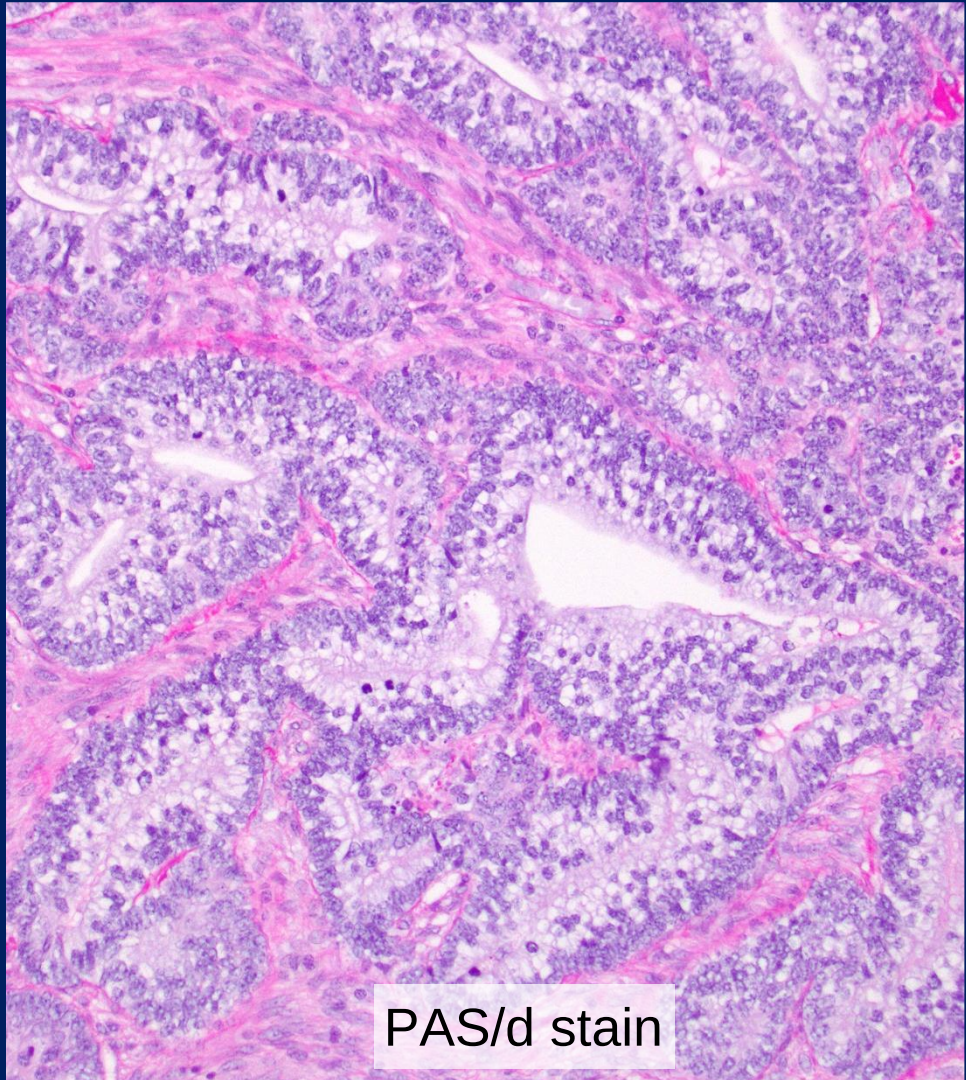
- Lung adenocarcinoma resembling developing fetal lung in its pseudoglandular stage
  - Complex glandular architecture with cytoplasmic clearing due to glycogen accumulation
- Low-grade tumor : unique entity characterized by *CTNNB1* mutations and morule formation
  - Younger age at presentation, no association with smoking, typically early stage at presentation and favorable patient outcomes
- High-grade tumor : high-grade adenocarcinoma
  - Commonly mixed with other patterns (<50%) including hepatoid, enteric, conventional adenocarcinomas and high-grade neuroendocrine

Koss MN, et al. Cancer 1991;67:2368-81, Nakatani Y et al. Am J Surg Pathol 1998;22:399-41, Suzuki M, et al. Histopathology 2015

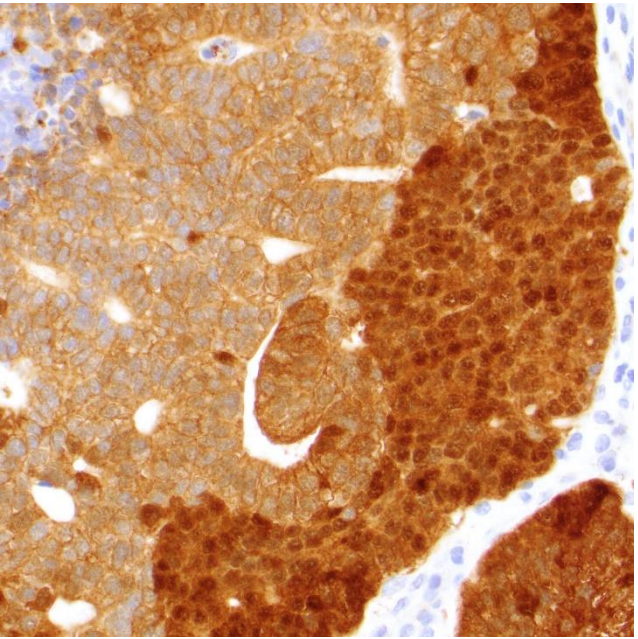
	Low-grade	High-grade
Prevalence	0.3%	0.5-1.4%
Age	Younger patients	Elderly patients
Sex	Female = Male	Female << Male
Smoking history	Not associated	Heavy smoking history +
Prognosis	Typically present at stage 1, favorable	Poor
Nuclear atypia	Minimal - mild	Significant, mitotic activity ++
Squamoid morules	+	-
Necrosis	Punctuated, if present	Broad areas
TTF-1 expression	Almost all+	50%
Aberrant β-catenin expression	+	-
NE marker expression	90%	50%
AFP, SALL4 and/or glypican 3 +	Rare	Common


Complex glandular architecture w/ cytoplasmic clearing
Morule formation

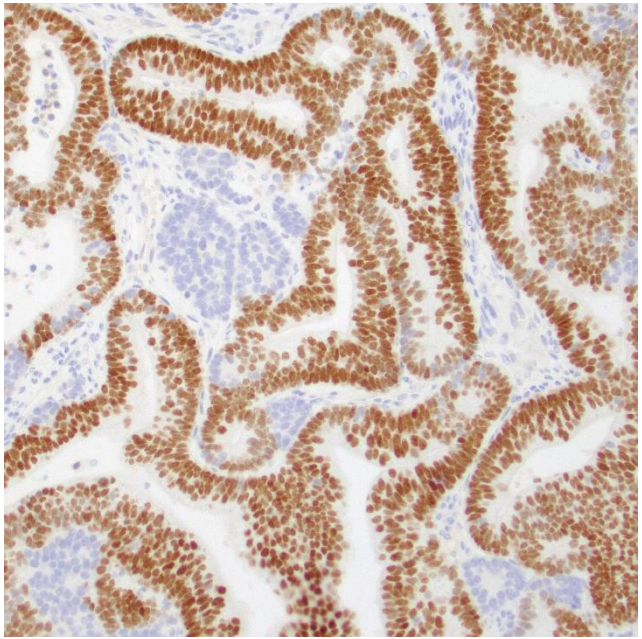

PAS stain


PAS/d stain

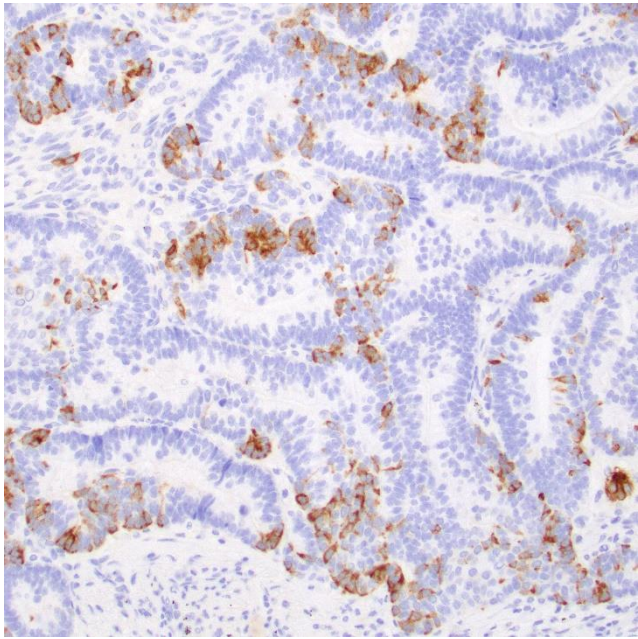
Low-Grade Fetal Adenocarcinoma



β-catenin



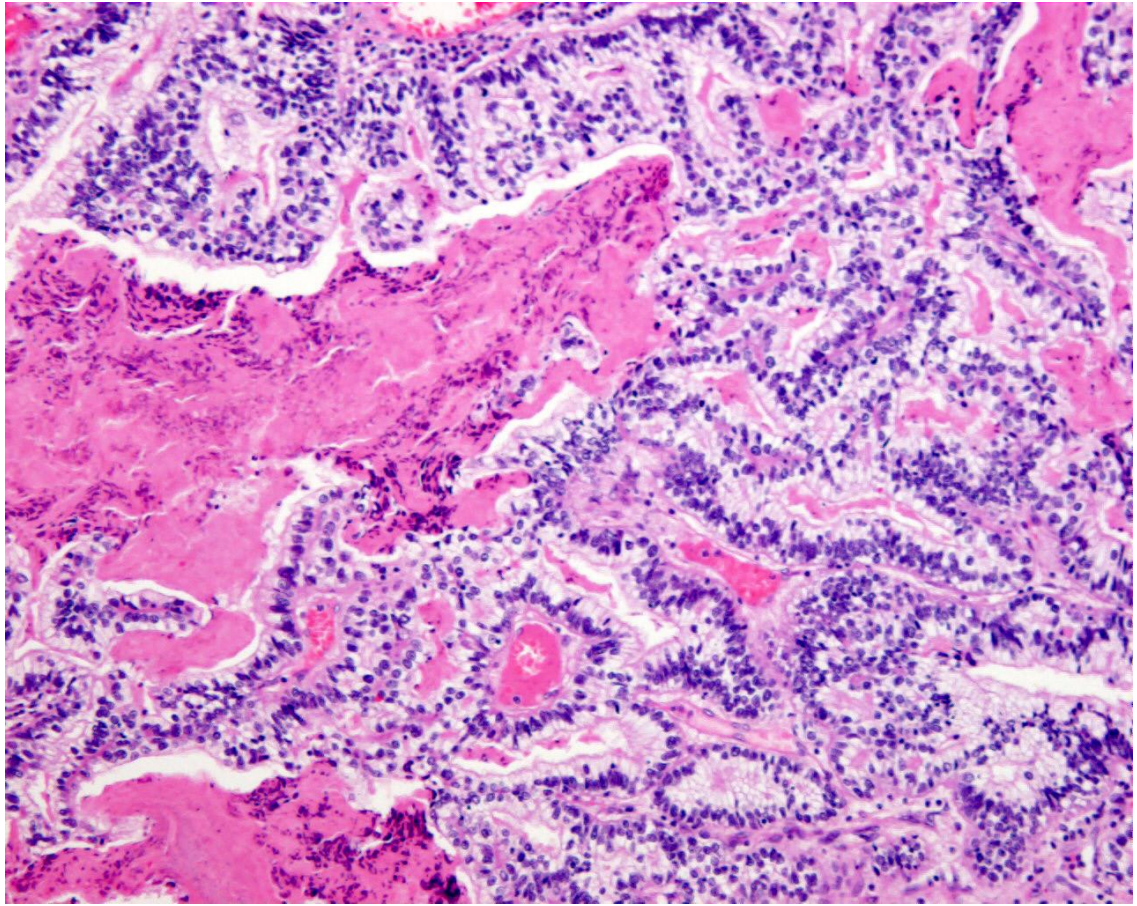
TTF-1

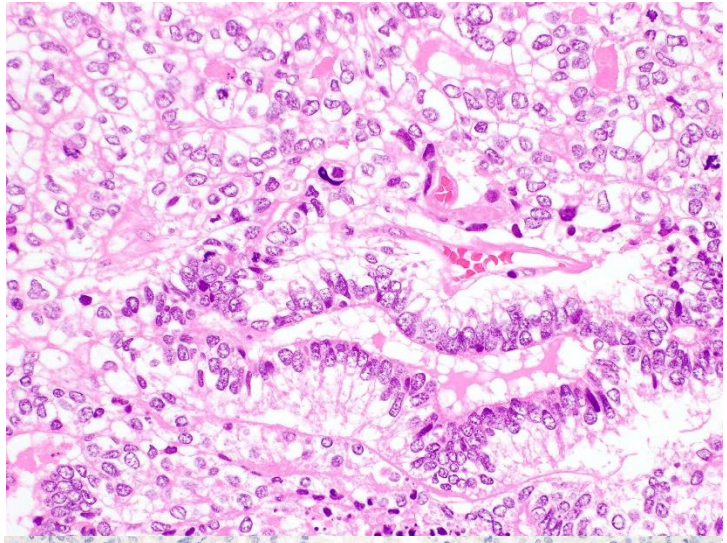


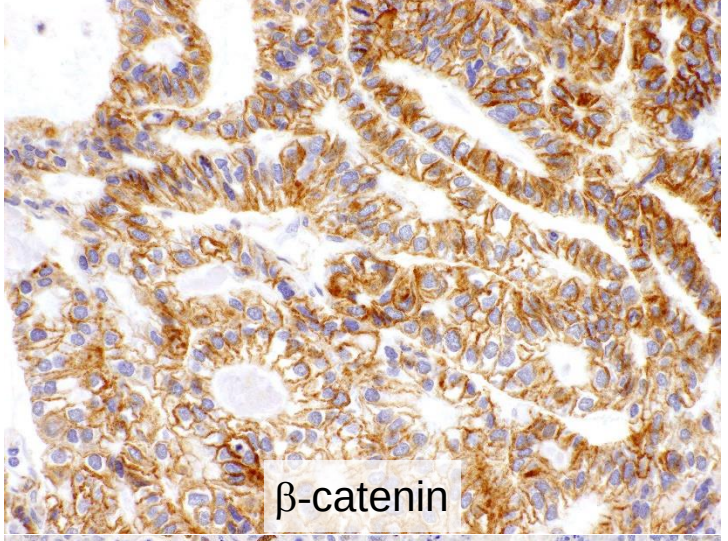
Synaptophysin

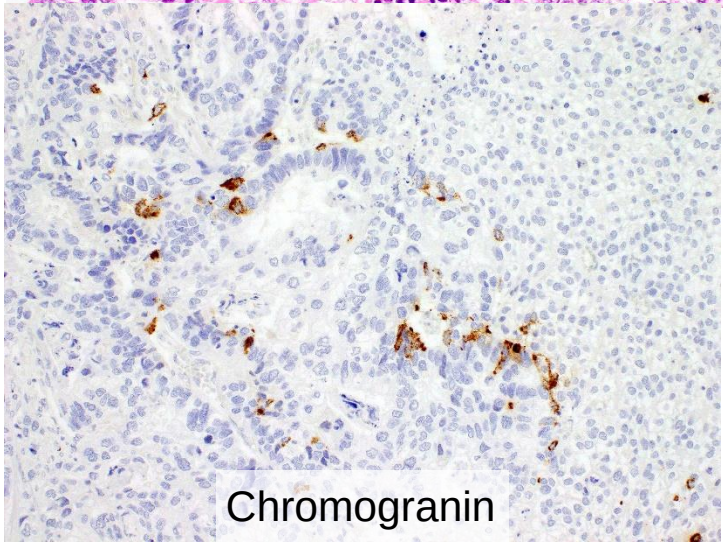
High-Grade Fetal Adenocarcinoma

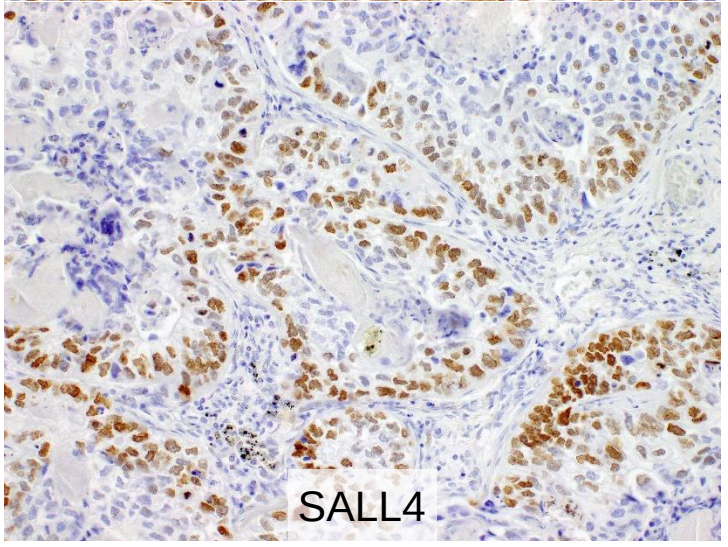
Courtesy of Dr. Yukio Nakatani






β-catenin


Chromogranin


SALL4

Differential Diagnosis

- Metastatic endometrioid carcinoma
  - PAX8 IHC
  - Clinical correlation for history of primary gynecological malignancy necessary
- Pulmonary blastoma
  - w/ prominent primitive mesenchymal component w/ increased atypia hyperchromatism and increased cellularity
- Carcinosarcoma with a high-grade fetal adenocarcinoma component

Differentiation between Lung Adenocarcinoma Variants and Metastasis from Extrapulmonary Sites

- Differentiation based on the followings could be challenging:
  - Morphology
  - Immunohistochemistry
  - Molecular profiling
  - Combination of thereof
- Clinicopathologic correlation is extremely important to differentiate between the two entities

Questions?

Rain forest in Costa Rica

Differentiation of Met from Pancreas vs. IMA

In comparison to IMA (n=39), metastatic pancreatic cancer (PDAC) cases (n=32) are characterized by:

- Fewer solitary lesions (95% vs. 15%; p = 0.0001)
- More tumors with pure (100%) mucinous morphology (23% vs. 50%; p = 0.0037)

Krasinskas A, Modern Pathol 2014

	CK20	CDX2	TTF-1	Napsin A	SMAD4 loss
IMA*	45-50%	45-50%	40-45%	25%	10% (ADC***)
Met from PDAC**	55%	50-50%	3%	0%	55%

* IMA: invasive mucinous adenocarcinoma, ** PDAC: pancreatic ductal adenocarcinoma, *** ADC: all lung adenocarcinomas

KRAS mutations, which are present in the vast majority (>90%) of PDAC, are also seen in > 2/3 of IMA

Krasinskas A, Modern Pathol 2014;27:262-70; Marchetti A, J Pathol 1996;199:254-9; Finberg KE, J Mol Diag 2007;9:320-6; Kadota K, Am J Surg Pathol 2014;38:1118-27; Shim HS, et al. J Thorac Oncol 2015;10(8):1156-62, MGH experience