

Immunohistochemical classification of the unknown primary tumour (UPT)

Part II

Prof. Mogens Vyberg
NordiQC
Institute of Pathology
Aalborg, Denmark

Secondary panels for **carcinoma** identification/subclassification

- Cell adhesion molecules
 - EpCAM
 - Claudin 4
- **Cytokeratin subtypes**
- Oncofetal proteins
- Transcription factors
- Neuroendocrine proteins
- Hormone receptors
- Secretory proteins
- . . .

- "GI-markers"
- "Fem.gen.tract markers"
- "Liver cell markers"
- Neuroendocrine cell markers
- "Breast markers"
- "Lung markers"
- "Urinary tract markers"
- Prostate markers
- Squamous cell markers
- "Mesothelial markers"
- "Adrenal cortical markers"
- Germinal cell markers

General epithelial markers:

Epithelial cell adhesion molecule (Ep-CAM)

Claudin 4

Ep-CAM

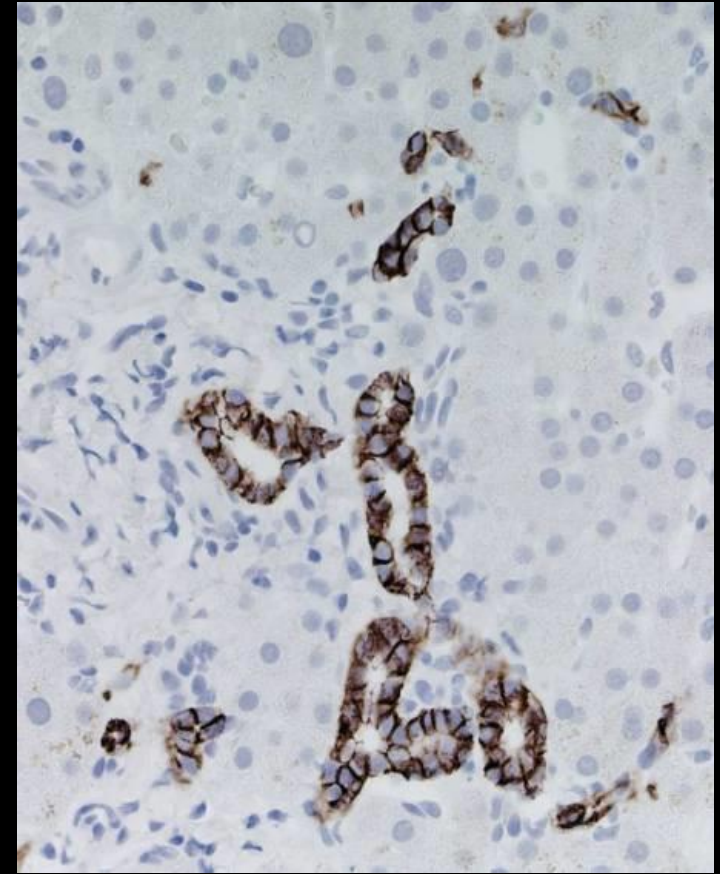
“Epithelial specific antigen”: Glycoproteins located on the cell membrane surface (preferentially basolaterally) and in the cytoplasm of **virtually all epithelial cells** with the exception of

- squamous epithelia (mucosae and reactive focal pos.)
- hepatocytes (pos. in reactive)
- renal proximal tubular cells
- gastric parietal cells
- some endocrine cells

Also negative

- mesothelial cells (pos. in reactive)
- mesenchymal cells
- germ cells
- neural crest cells
(except. olfactory neurons)

Liver



Ep-CAM

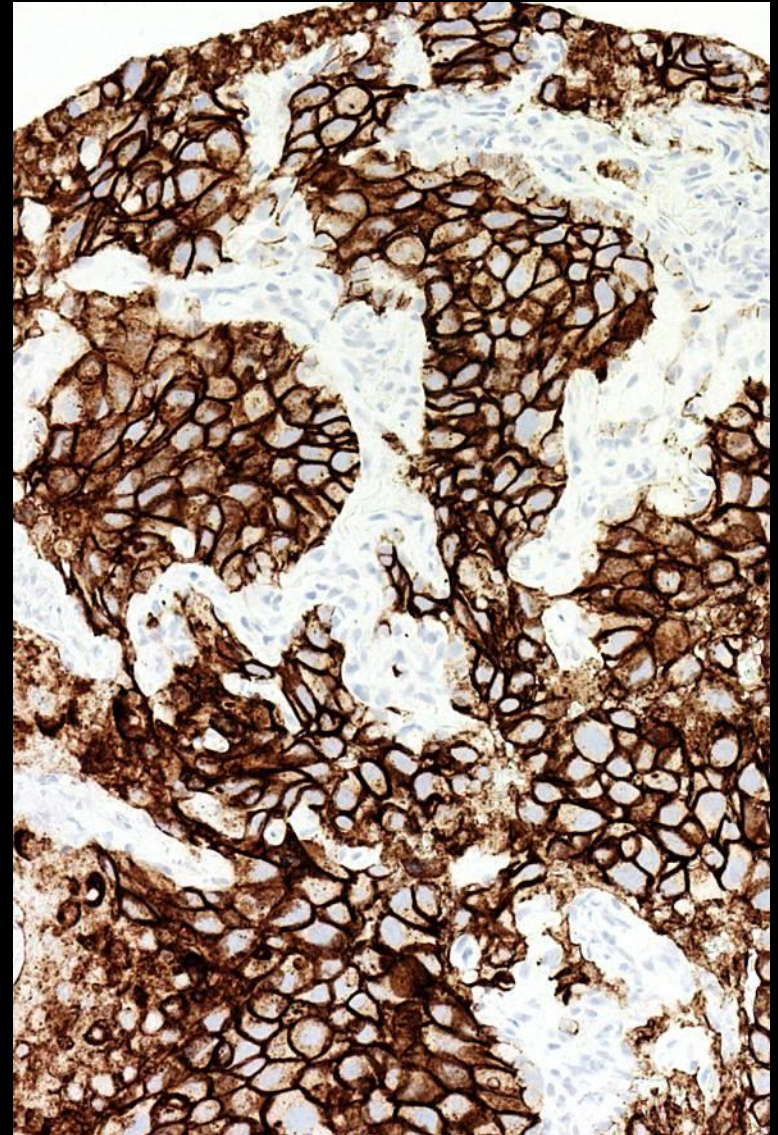
Often overexpressed in malignancies

+

- Adenocarcinomas (of most types)
- Neuroendocrine neoplasms

+/-

- Germinal cell tumours
 - (seminoma weak)
- Synovial sarcoma
- Brenner tumour
- Desmoplastic small cell tumour
- Olfactory neuroblastoma

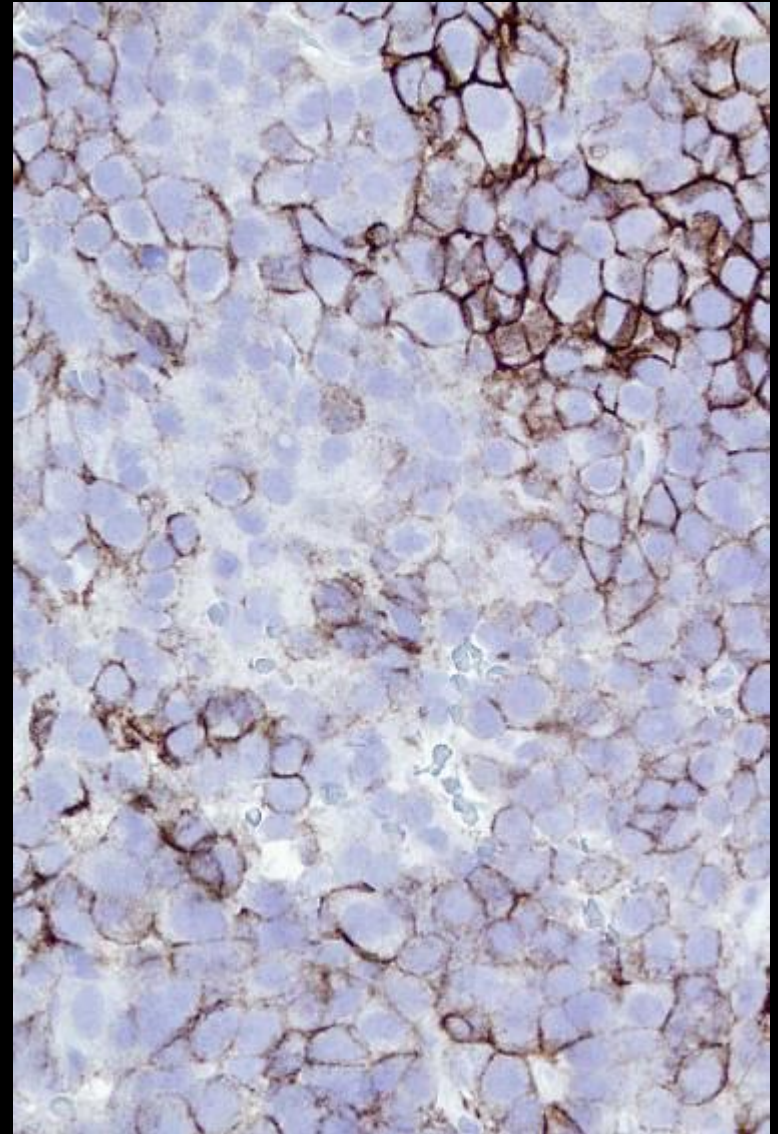


Large cell lung carcinoma

Ep-CAM

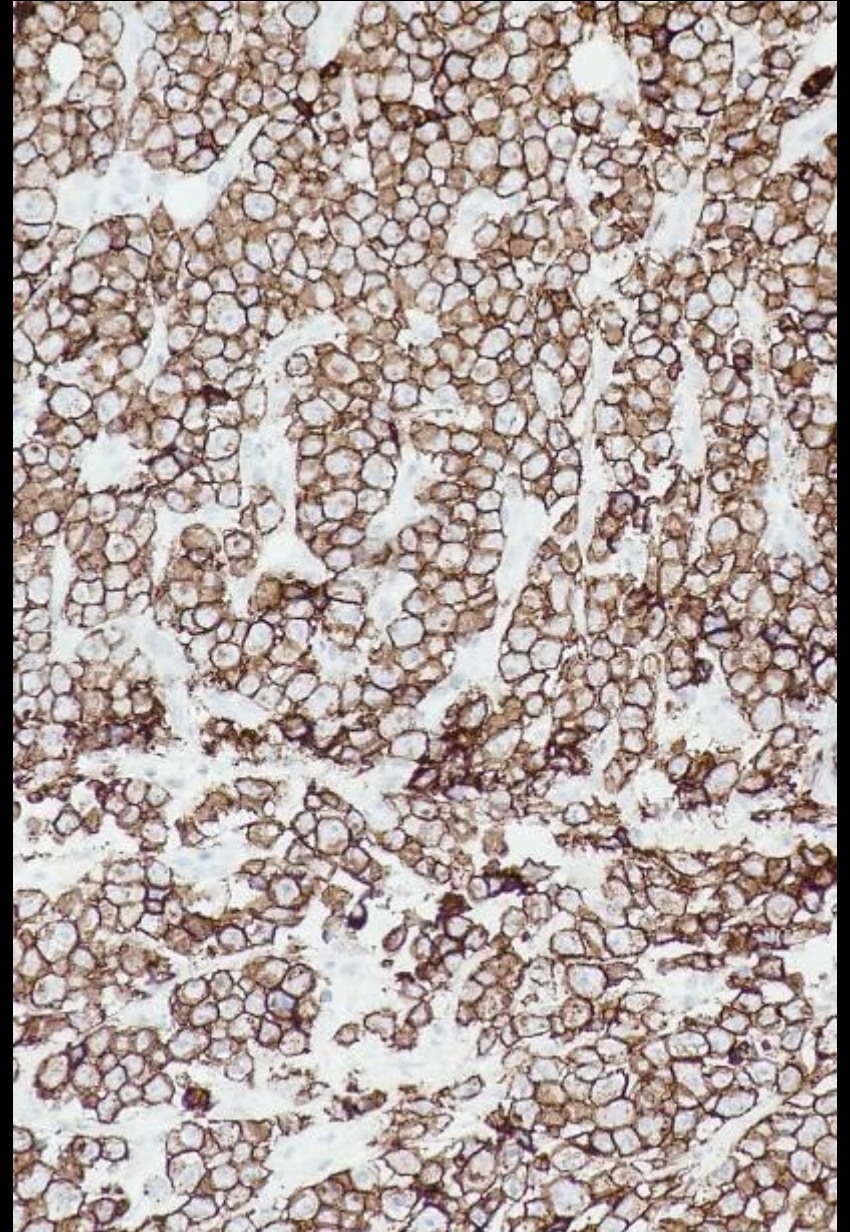
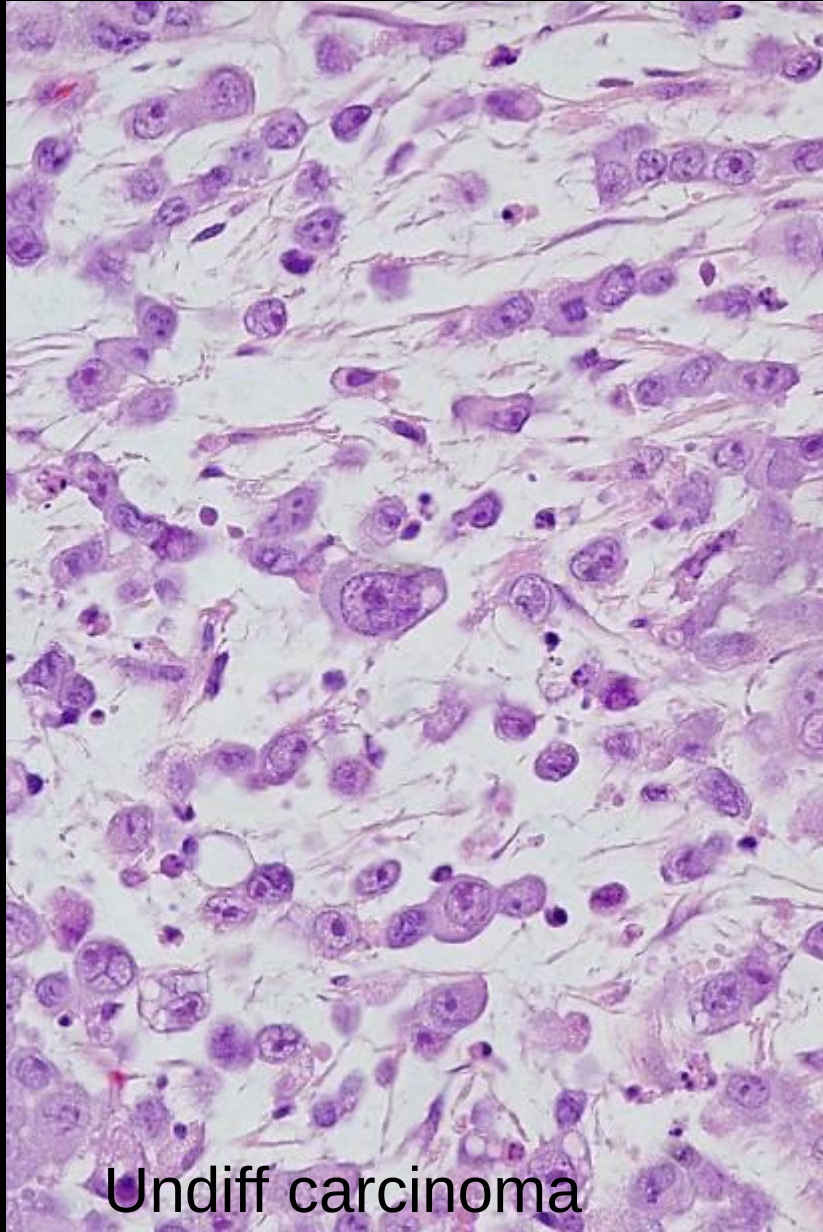
-/+

- Lobular breast carcinoma
- Hepatocellular carcinoma
- Squamous cell carcinoma
- Renal cell carcinoma
- Malignant mesothelioma
-
- Adrenal cortical carcinoma
- Choroid plexus pap./carcinoma
- Sarcomas (apart from synovial)
- Lymphomas



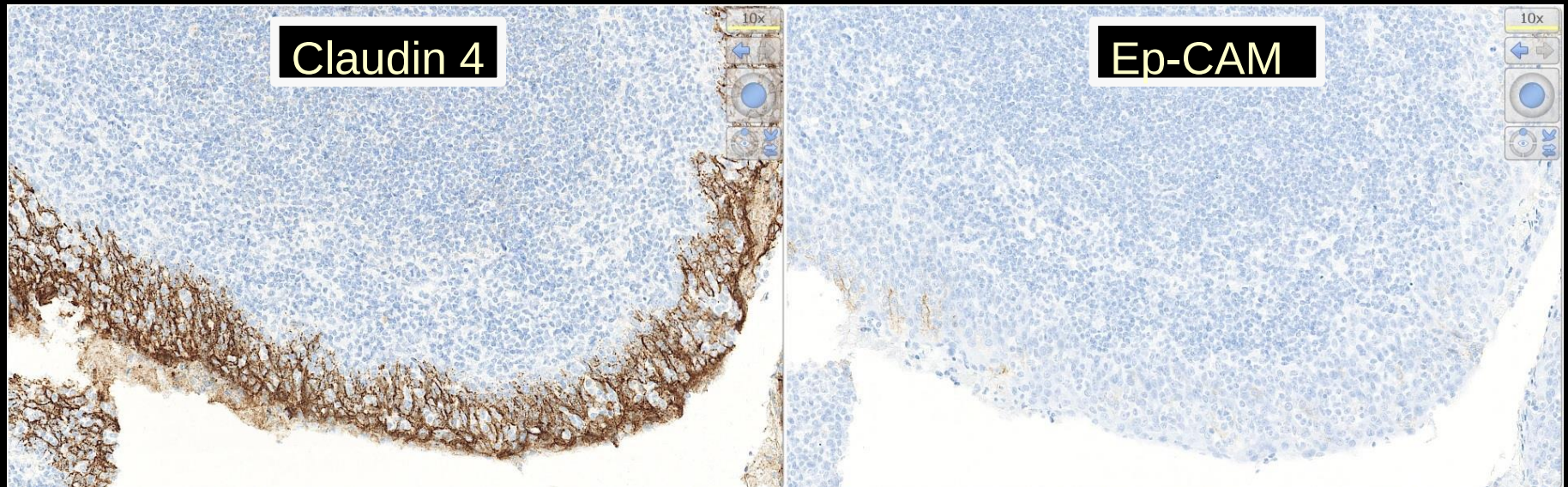
HCC

Ep-CAM



Claudin 4

Integral membrane protein, which belongs to the claudin family. The protein is a component of **tight junction** strands and may play a role in internal organ development and function.



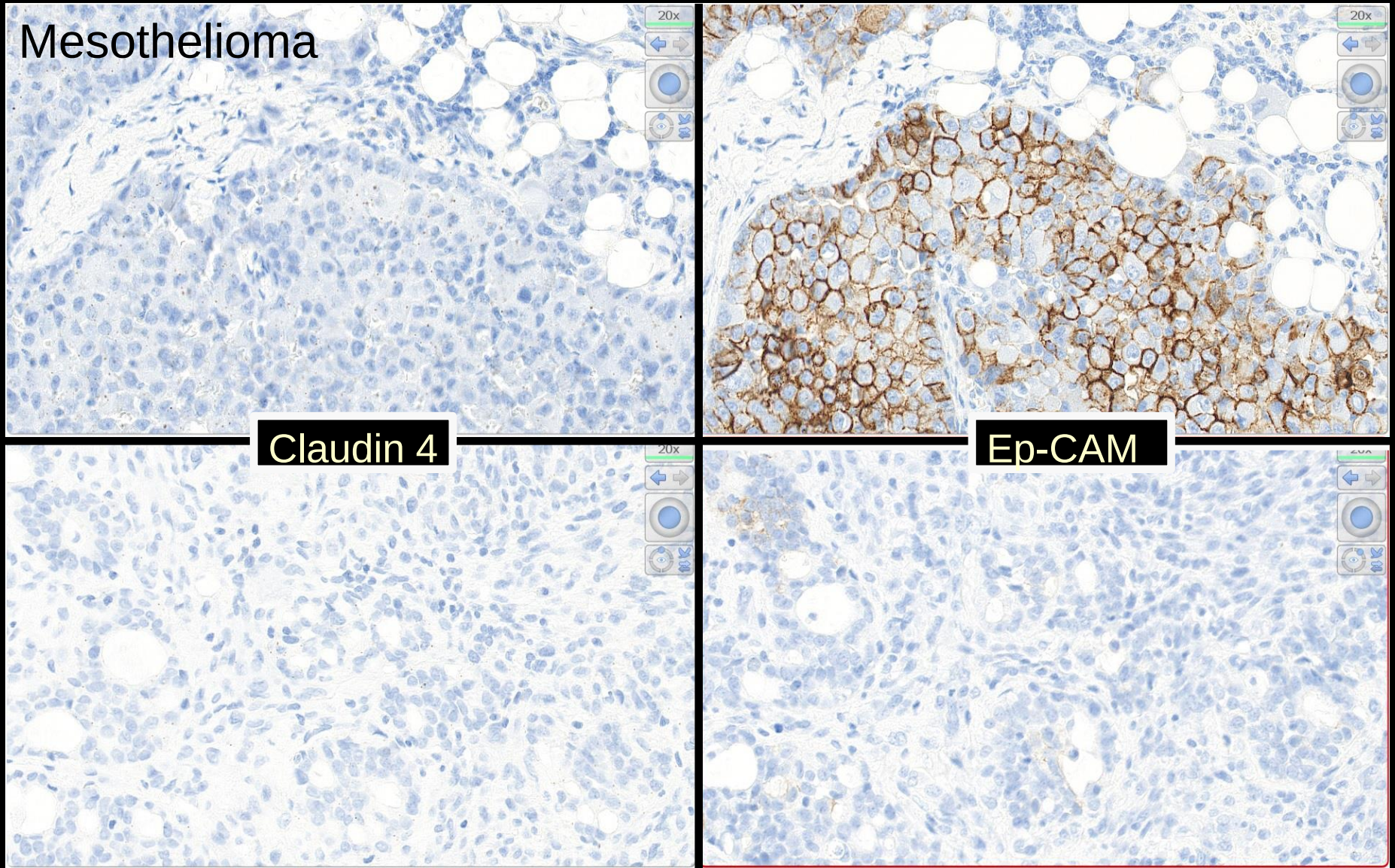
Tonsil

Claudin 4 vs. Ep-CAM

Mesothelioma

Claudin 4

Ep-CAM



Cytokeratins – a multigene family

- Highly complex family of intermediate filaments
- > 50 distinct types (excl. trichocytic keratins)
- Types CK1-20 diagnostically most relevant:

Class I (type A - Acidic):

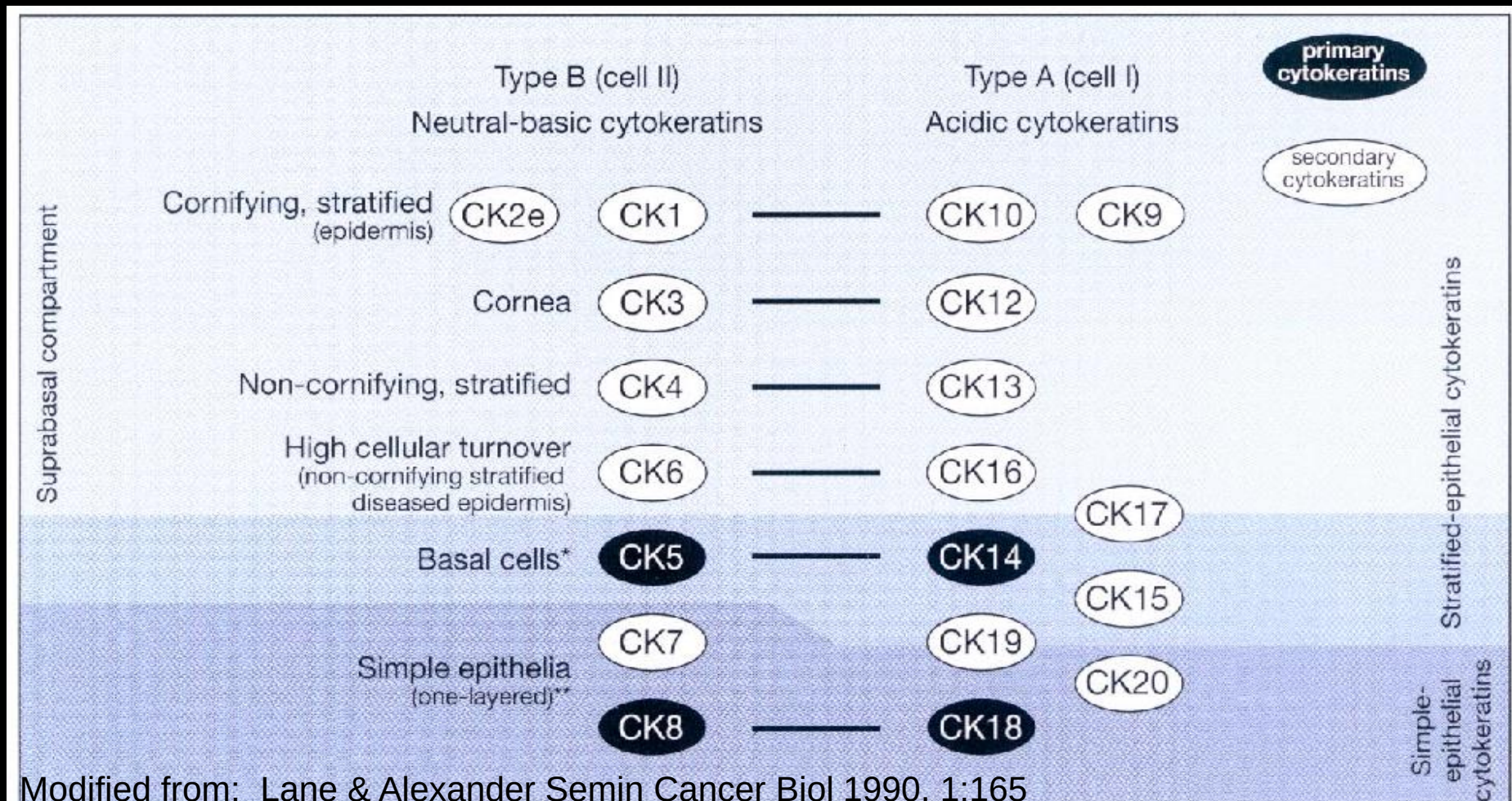
- CK9 (64 kDa) - CK20 (40 kDa)

Class II (type B - Basic/neutral):

- CK1 (68 kDa) - CK8 (52.5 kDa)

Pairing of cytokeratins

- One CK class I and one CK class II 'always' paired
- CK class I in a pair ~ 8 kDa smaller than class II



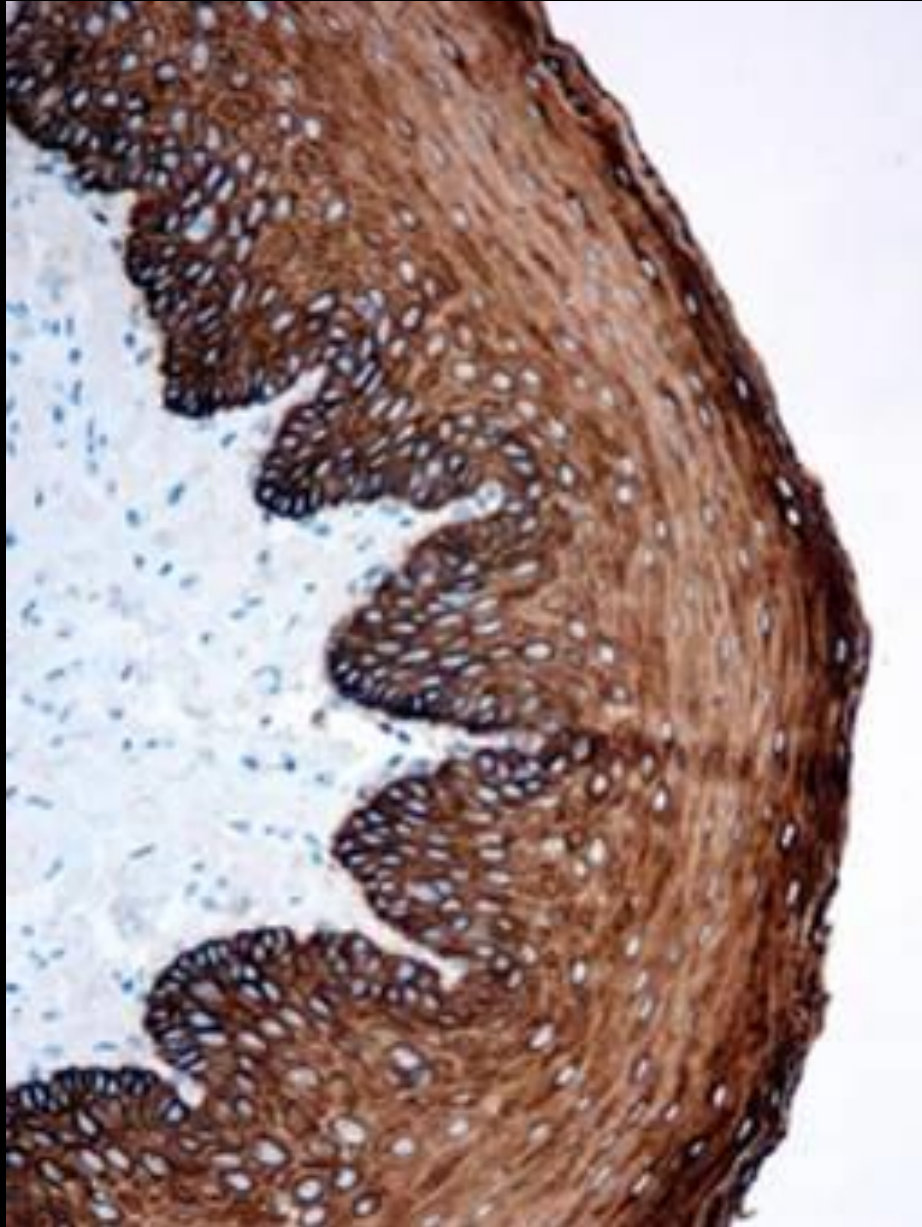
Cytokeratin types and cell types

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	+++	+++	(+) ¹	(++) ¹²	(+) ¹	-	(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

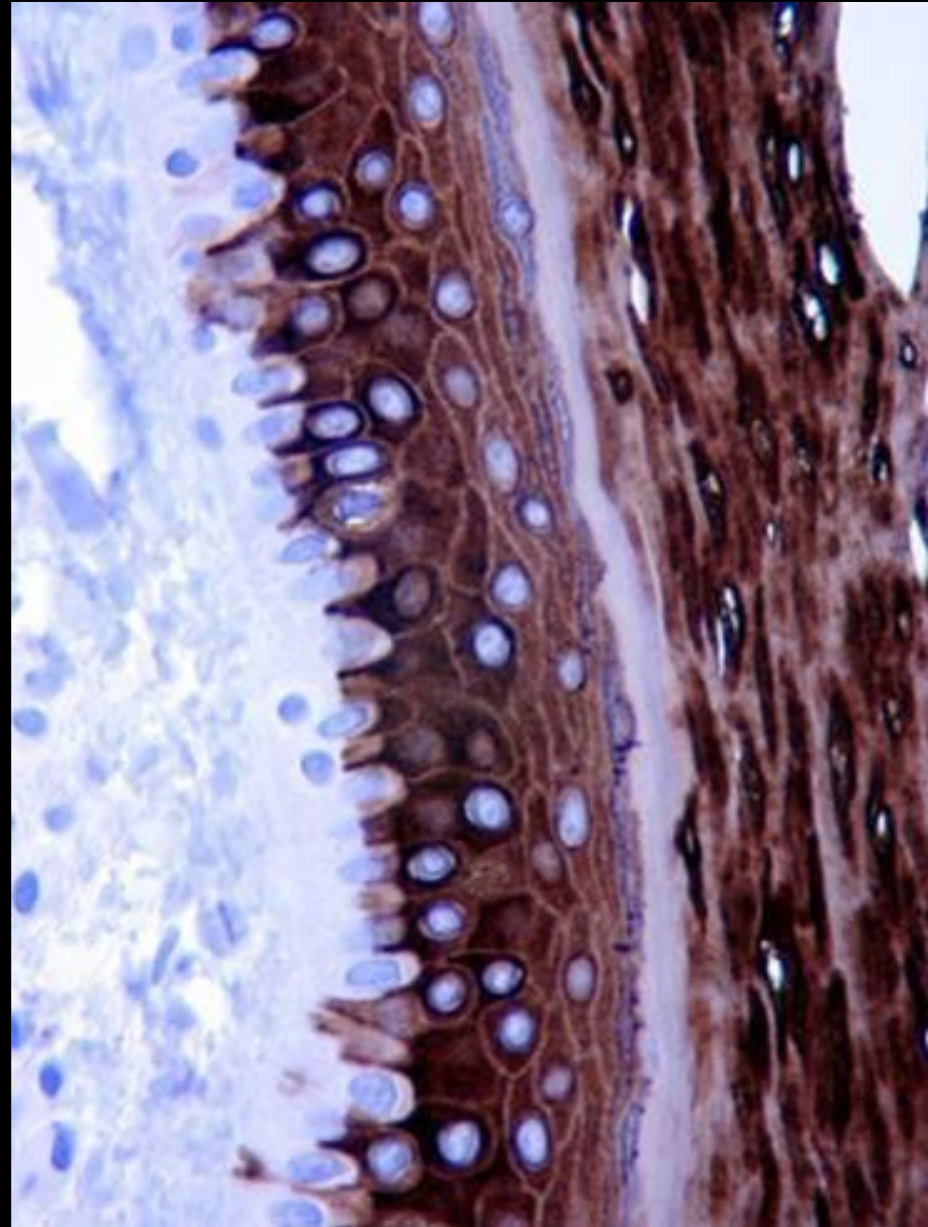
HMW Cytokeratin types - squamous epithelia

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	+++	+++	(+) ¹	(++) ¹²	(+) ¹	-	(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

HMW Cytokeratin types - squamous epithelia



CK5: esophagus

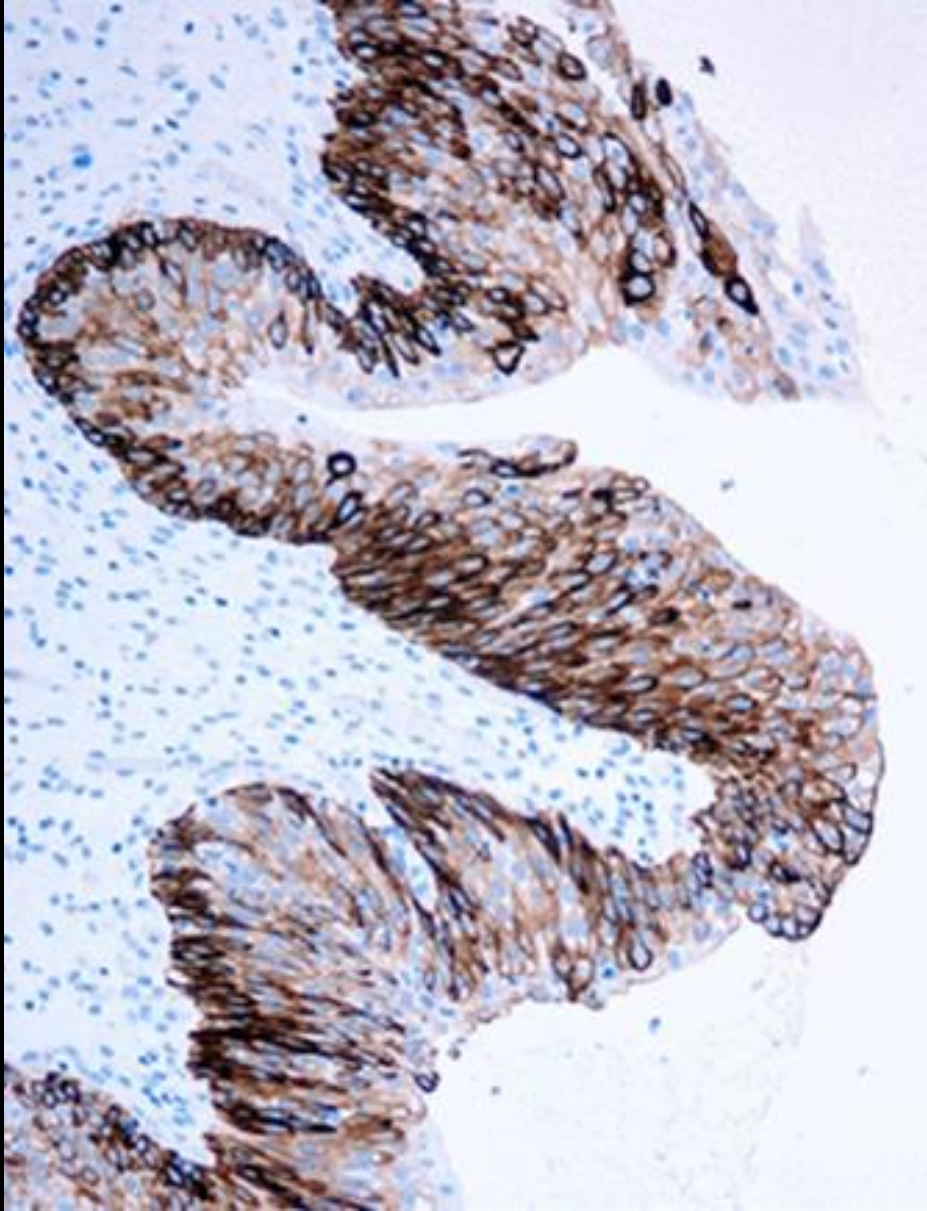


CK4: esophagus

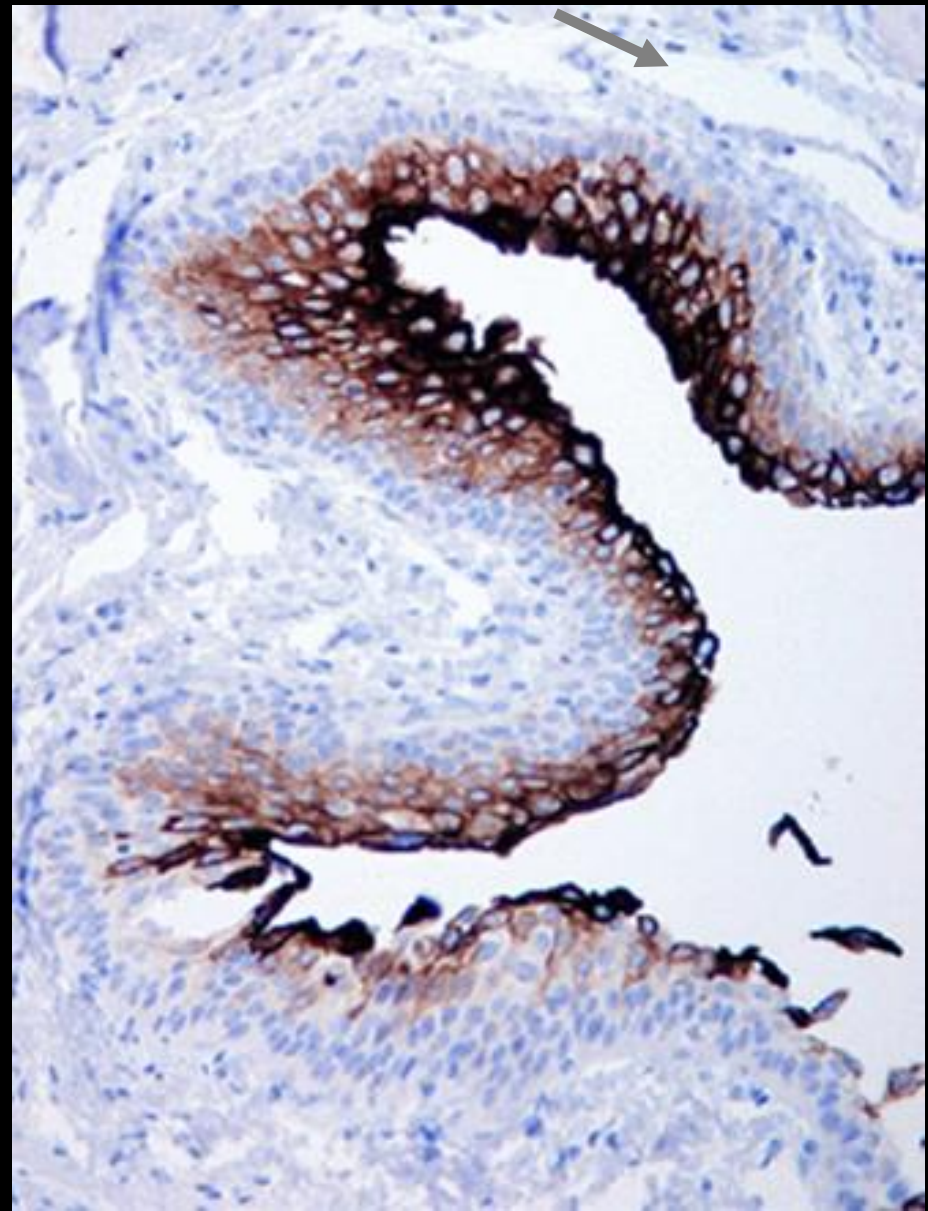
Cytokeratin types - urothelium

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	+++	+++	(+) ¹	(++) ¹²	(+) ¹	-	(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++)	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - urothelium



CK5 (+CK13)

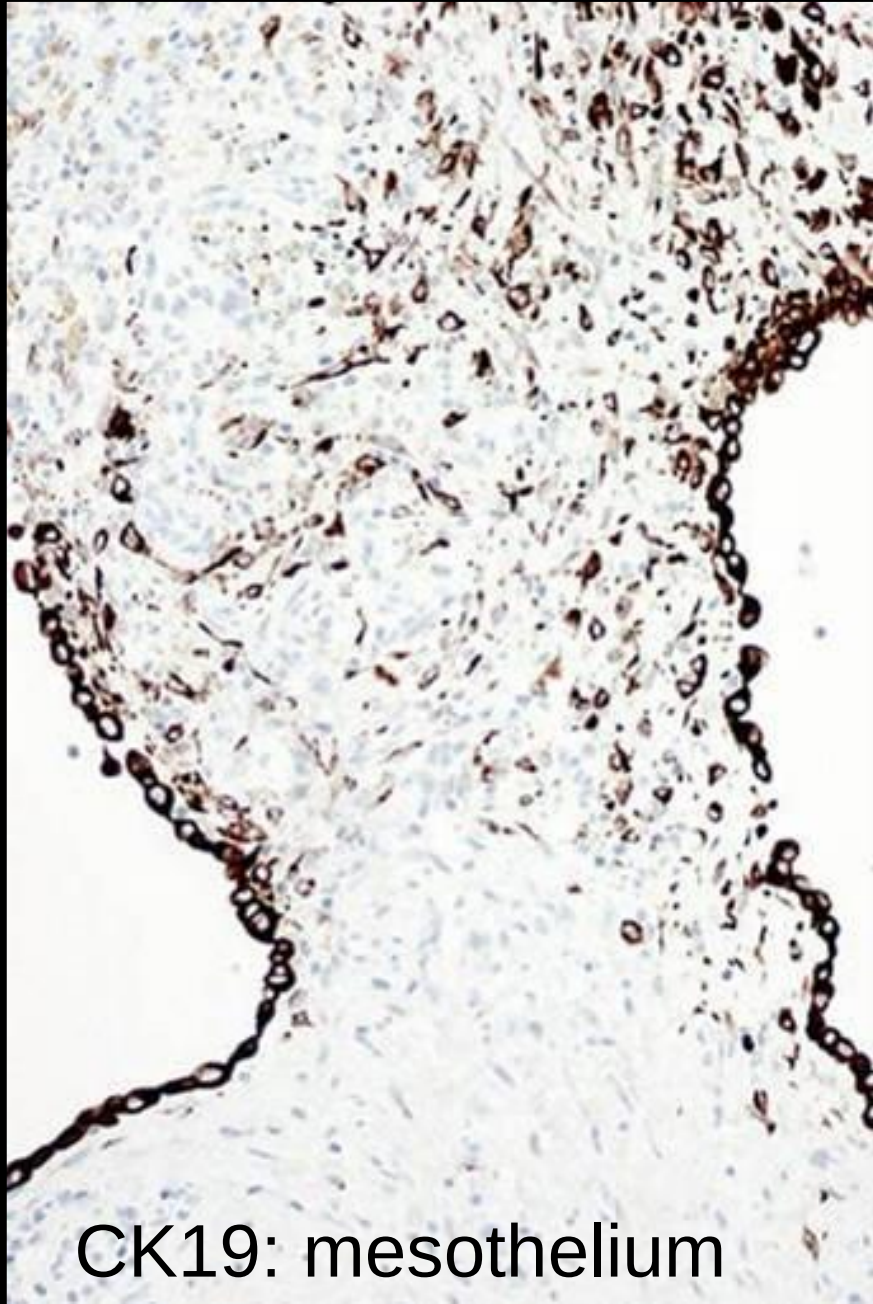


CK20

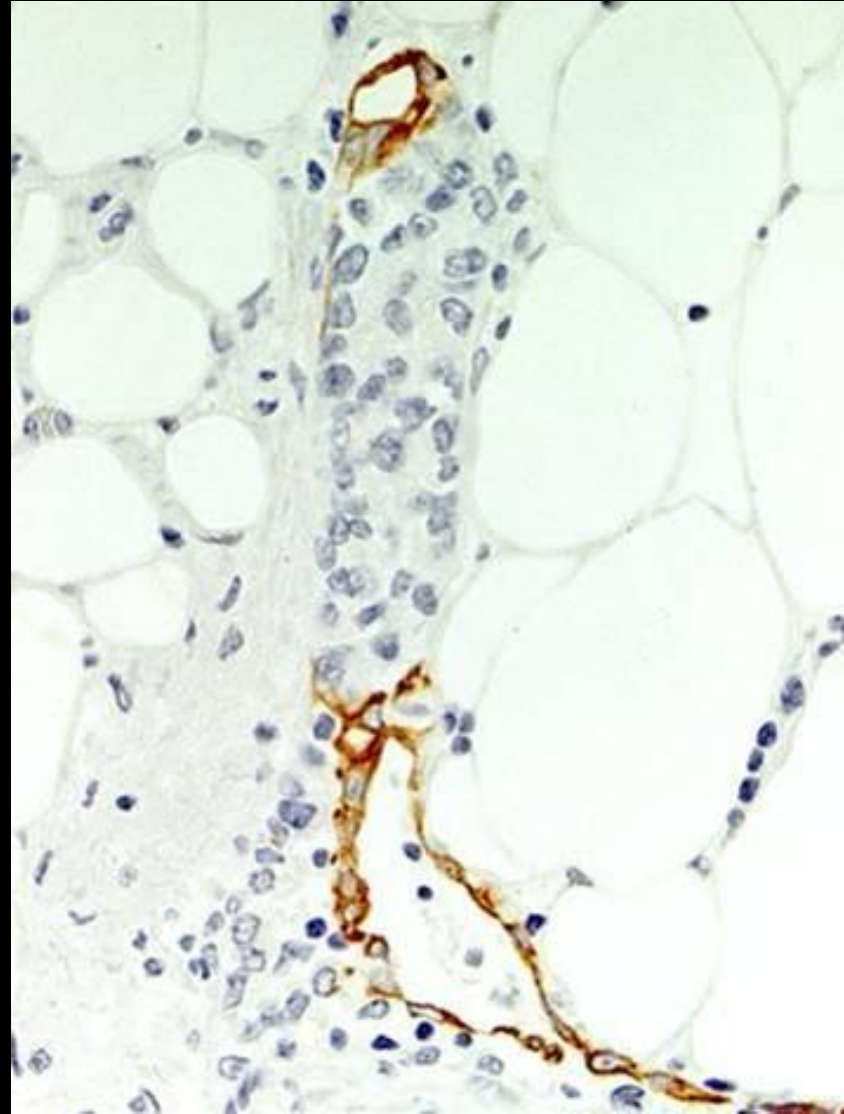
Cytokeratin types - mesothelium

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	(+)	-	-	-	-
- suprabasal, non-keratiniz.ep.	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	+++	+++	(+) ¹	(++) ¹²	(+) ¹	-	(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - mesothelium



CK19: mesothelium

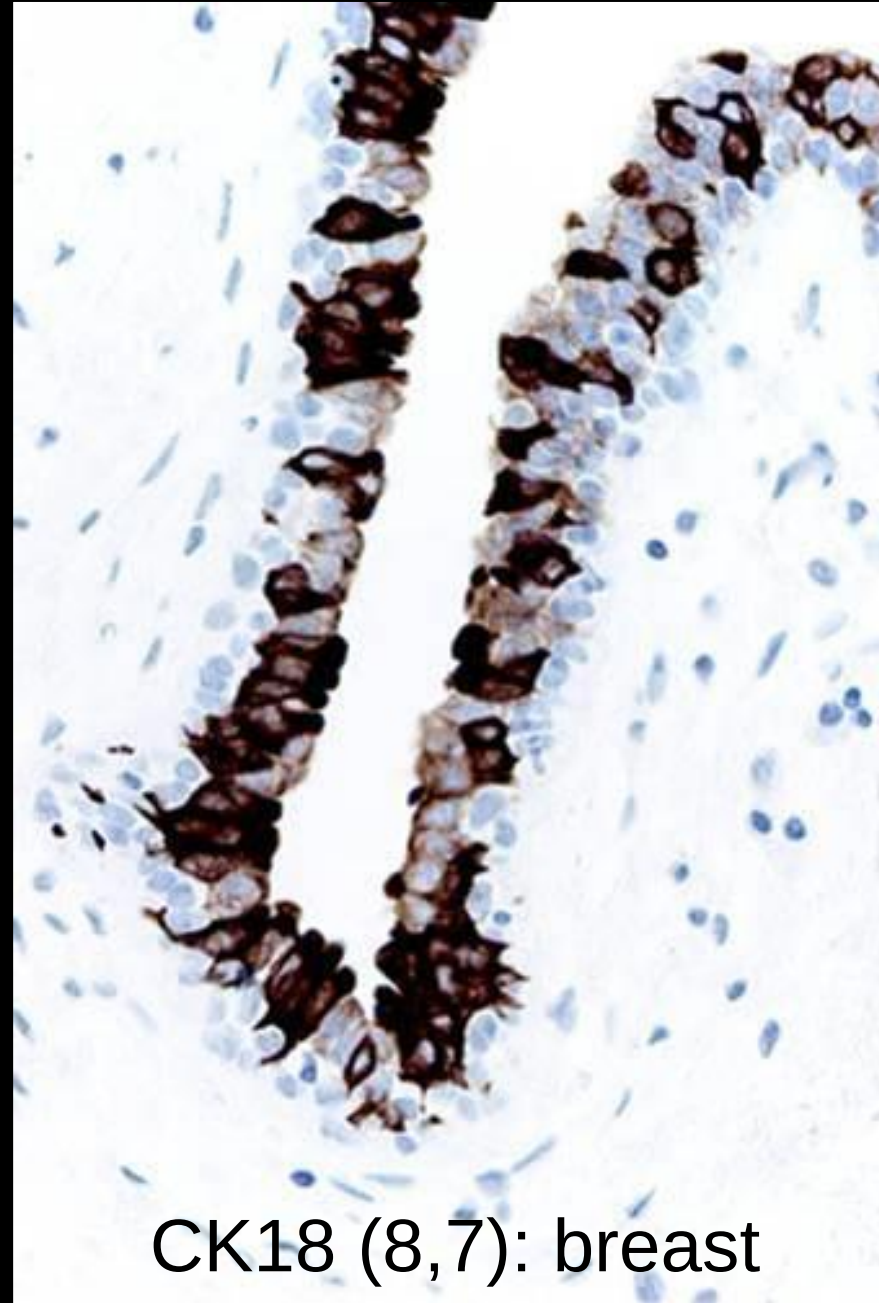
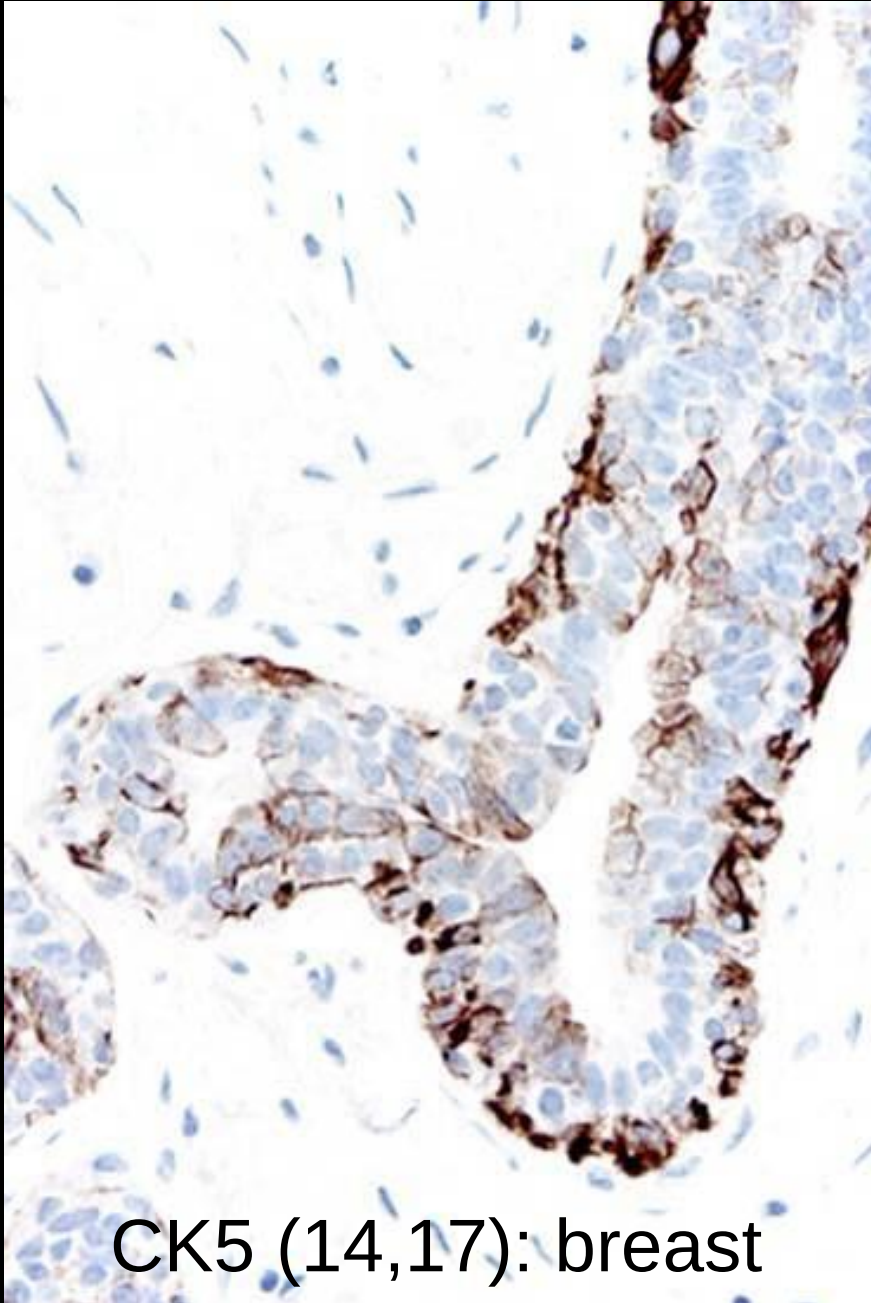


CK5: mesothelium
(adenocarcinoma neg.)

Cytokeratin types - complex epithelia

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	(+) ¹	(++) ¹²	(+) ¹	-	(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

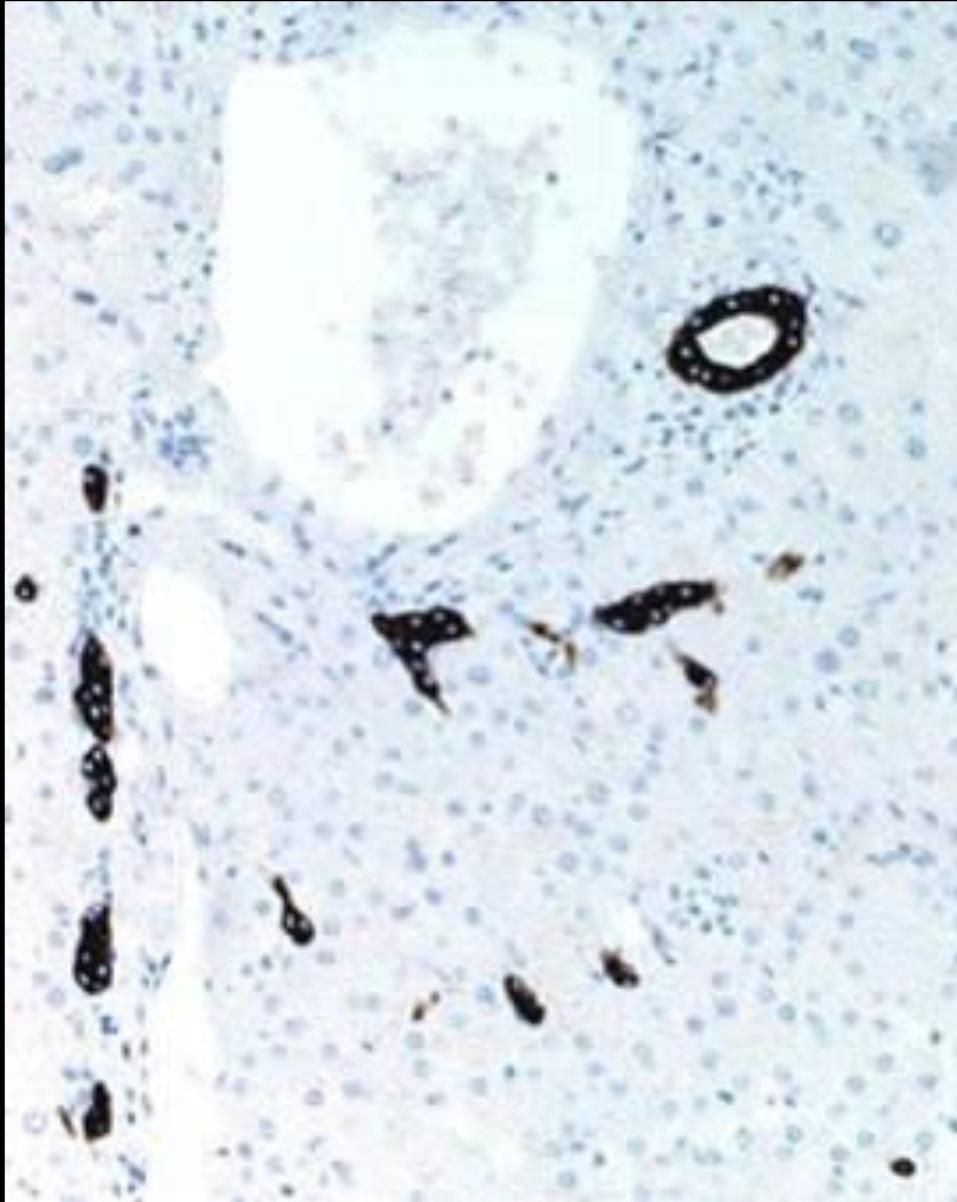
Cytokeratin types - complex epithelia



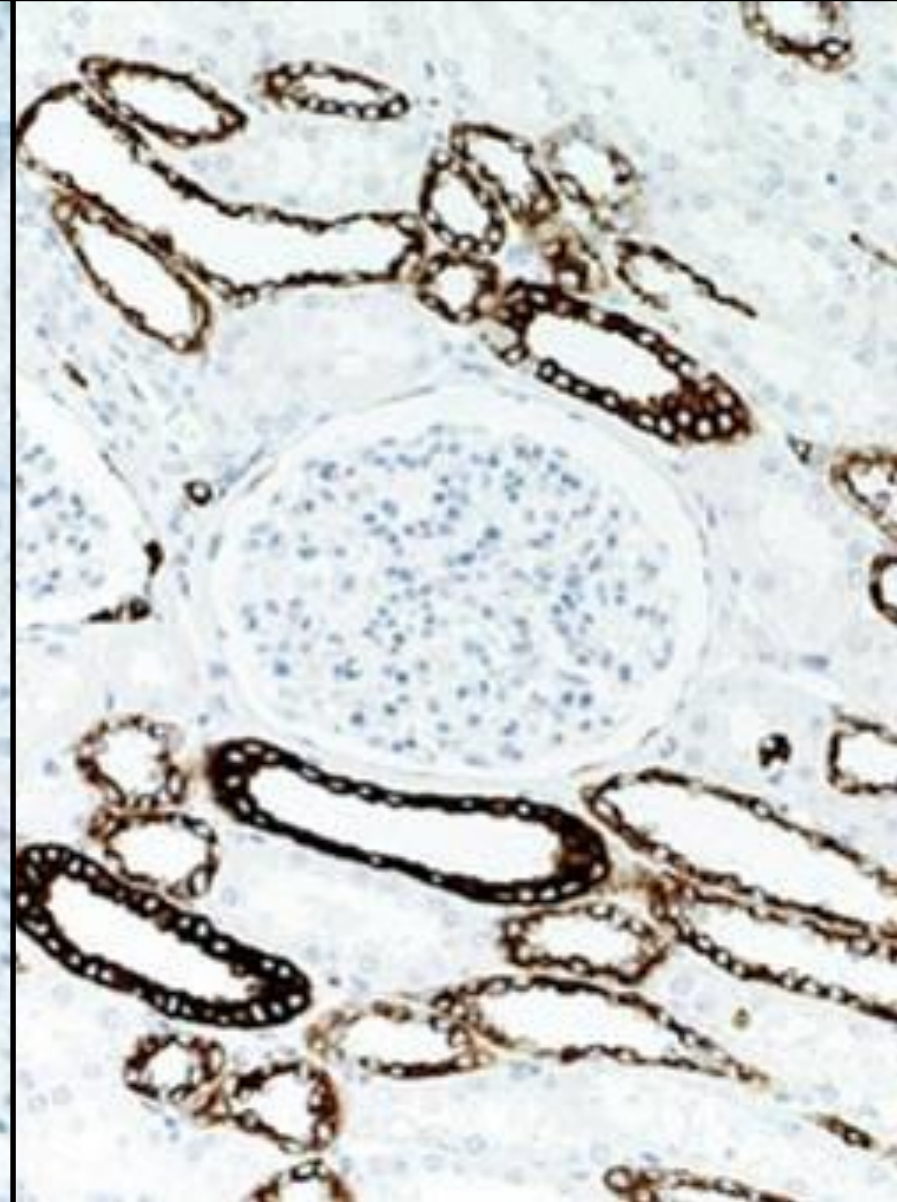
Cytokeratin types - simple epithelia

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) ¹	-	-(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - simple epithelia (liver, kidney)



CK7(19): bile ducts

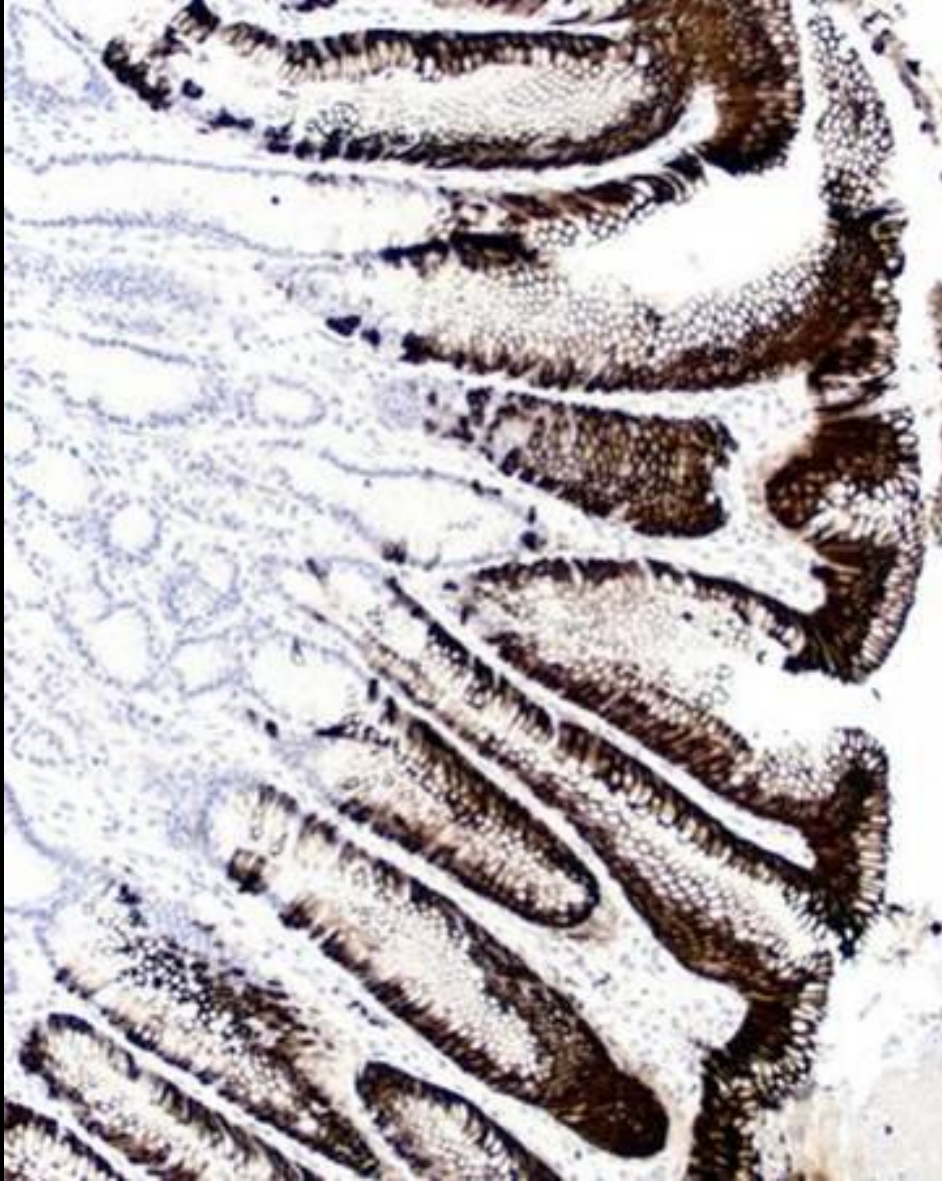


CK7(19): renal col.

Cytokeratin types - simple epithelia

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) ¹	-	-(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - simple epithelia



CK20: gastric foveolae

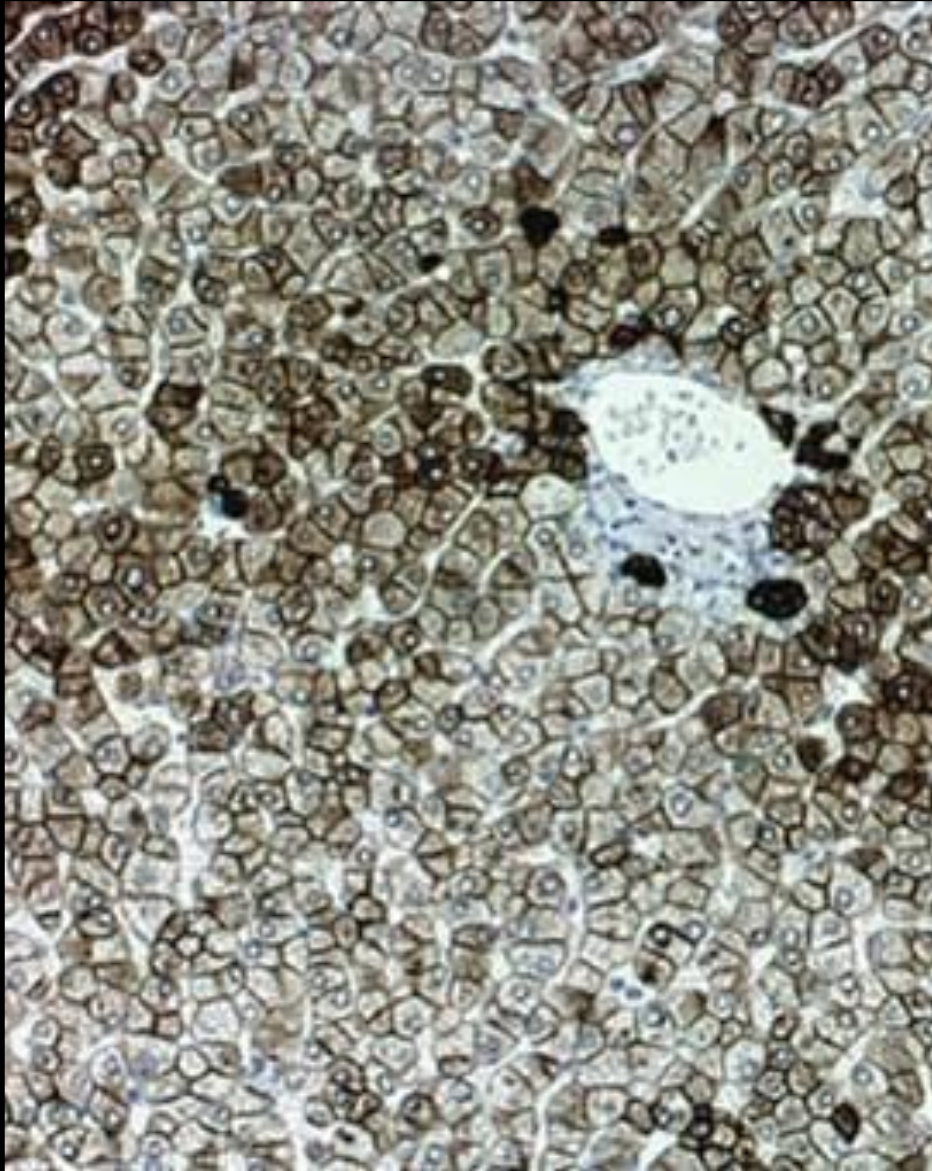


CK20: colon

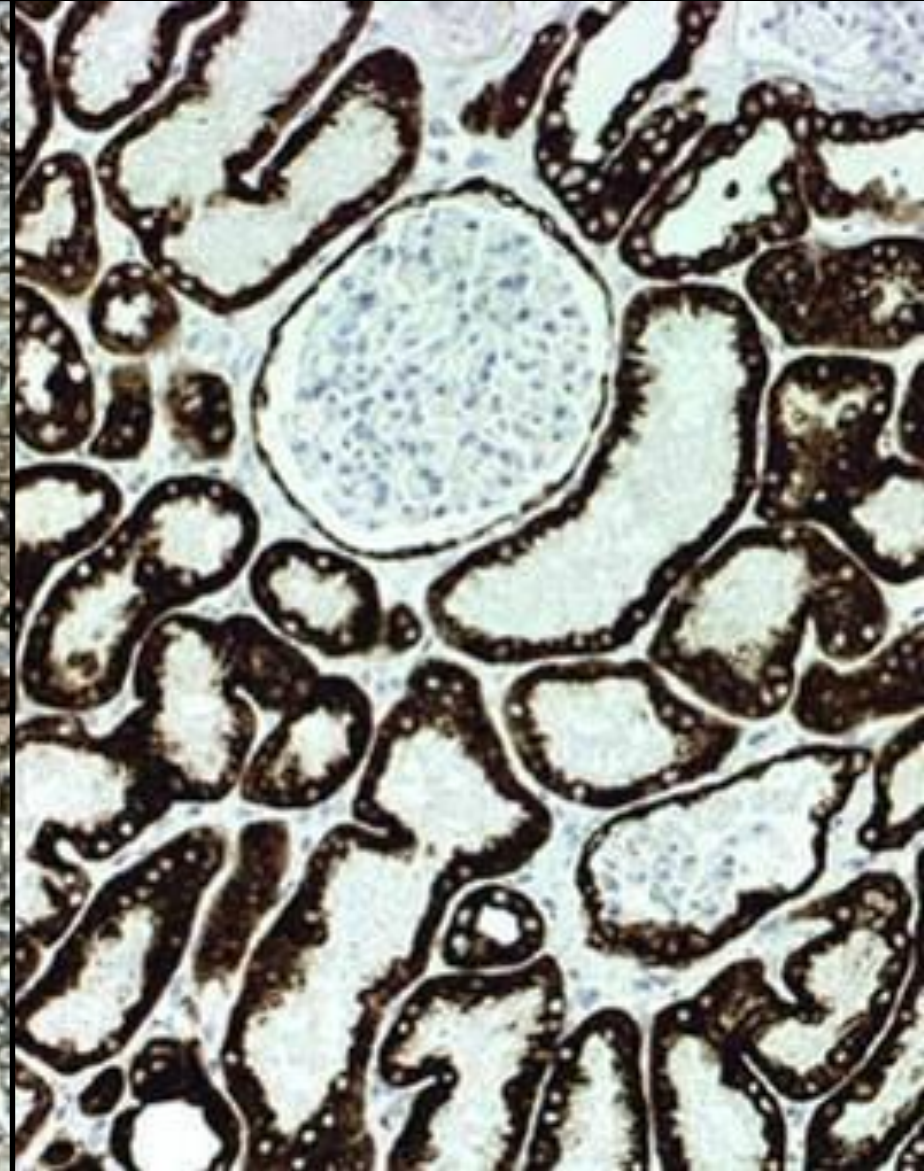
Cytokeratin types - simple epithelia

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) ¹	-	-(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - simple epithelia



CK8: liver

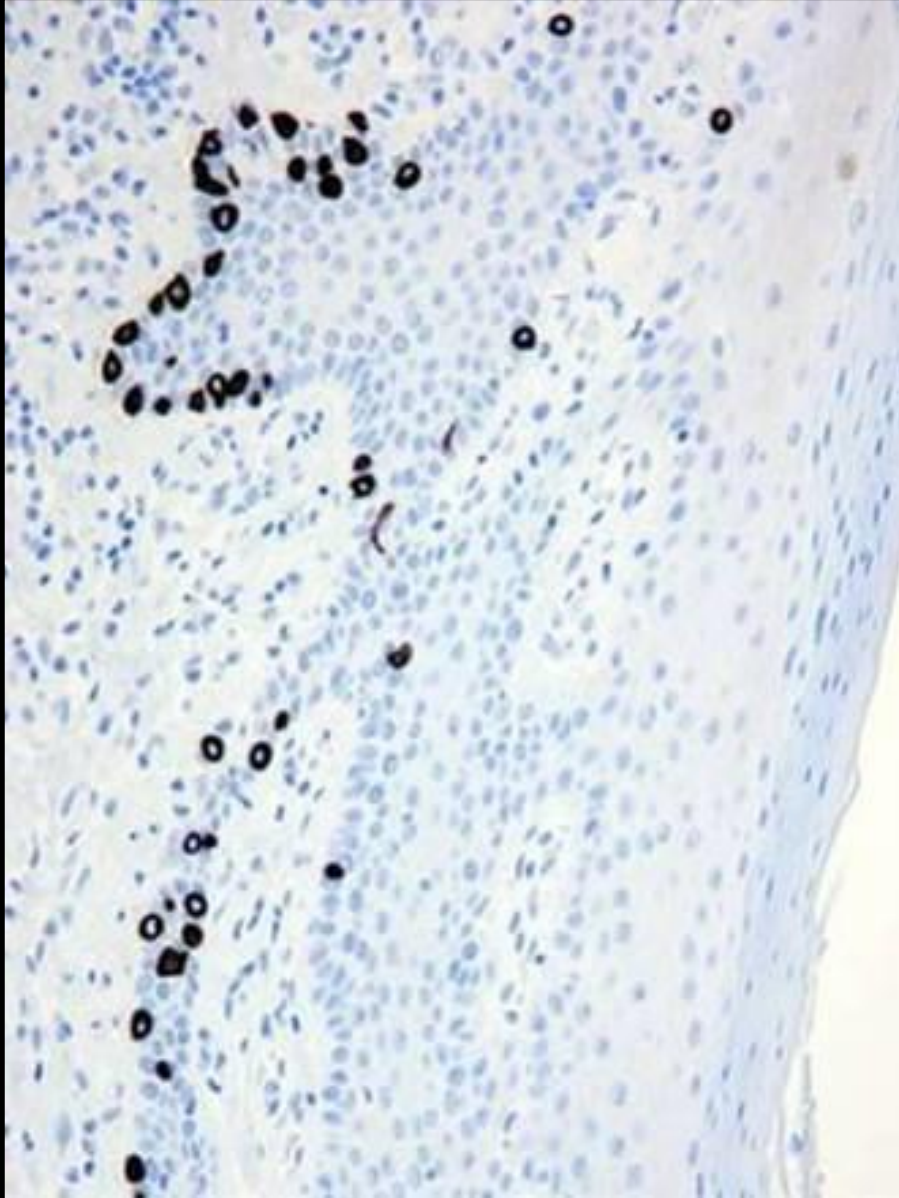


CK8: kidney

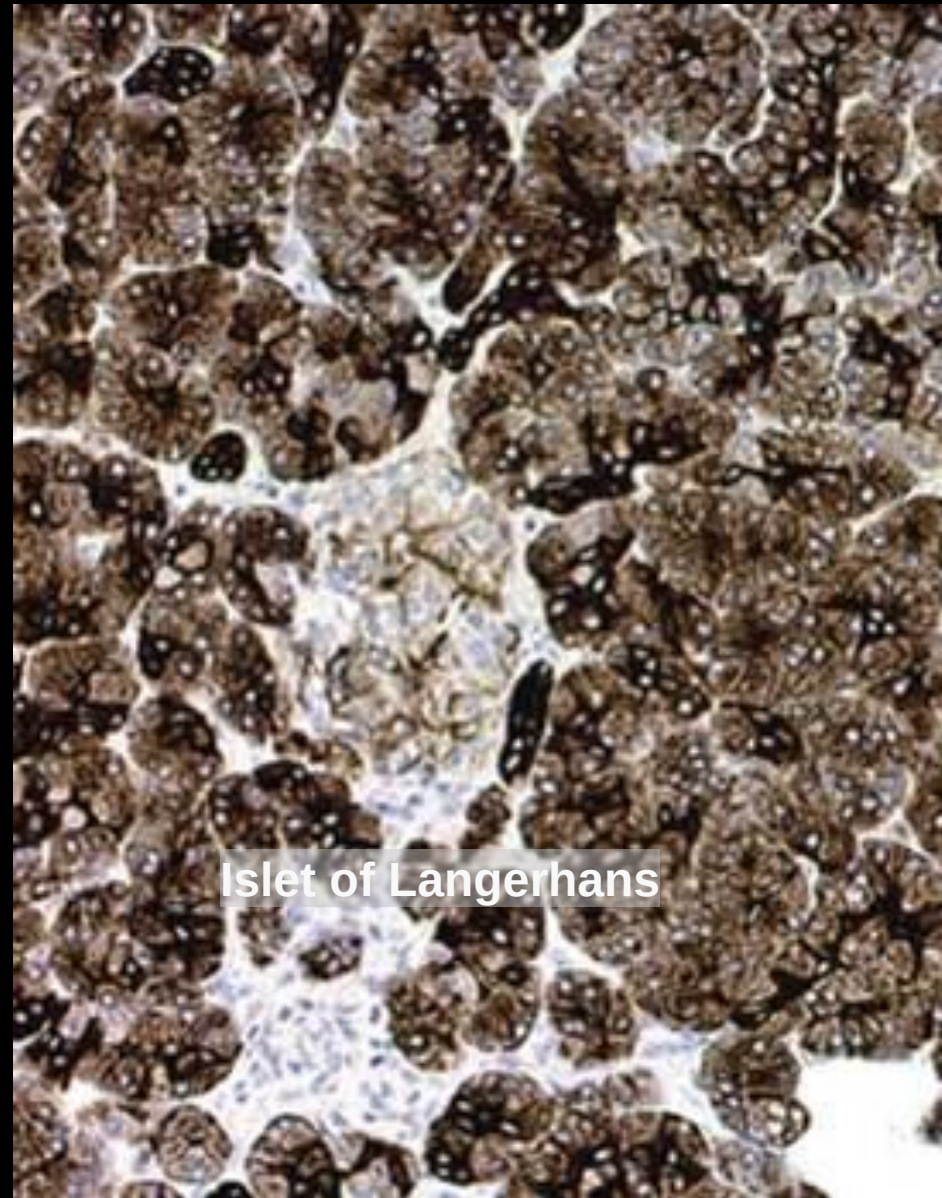
Cytokeratin types - simple epithelia

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) ¹	-	-(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - simple epithelia



CK20: Merkel cells

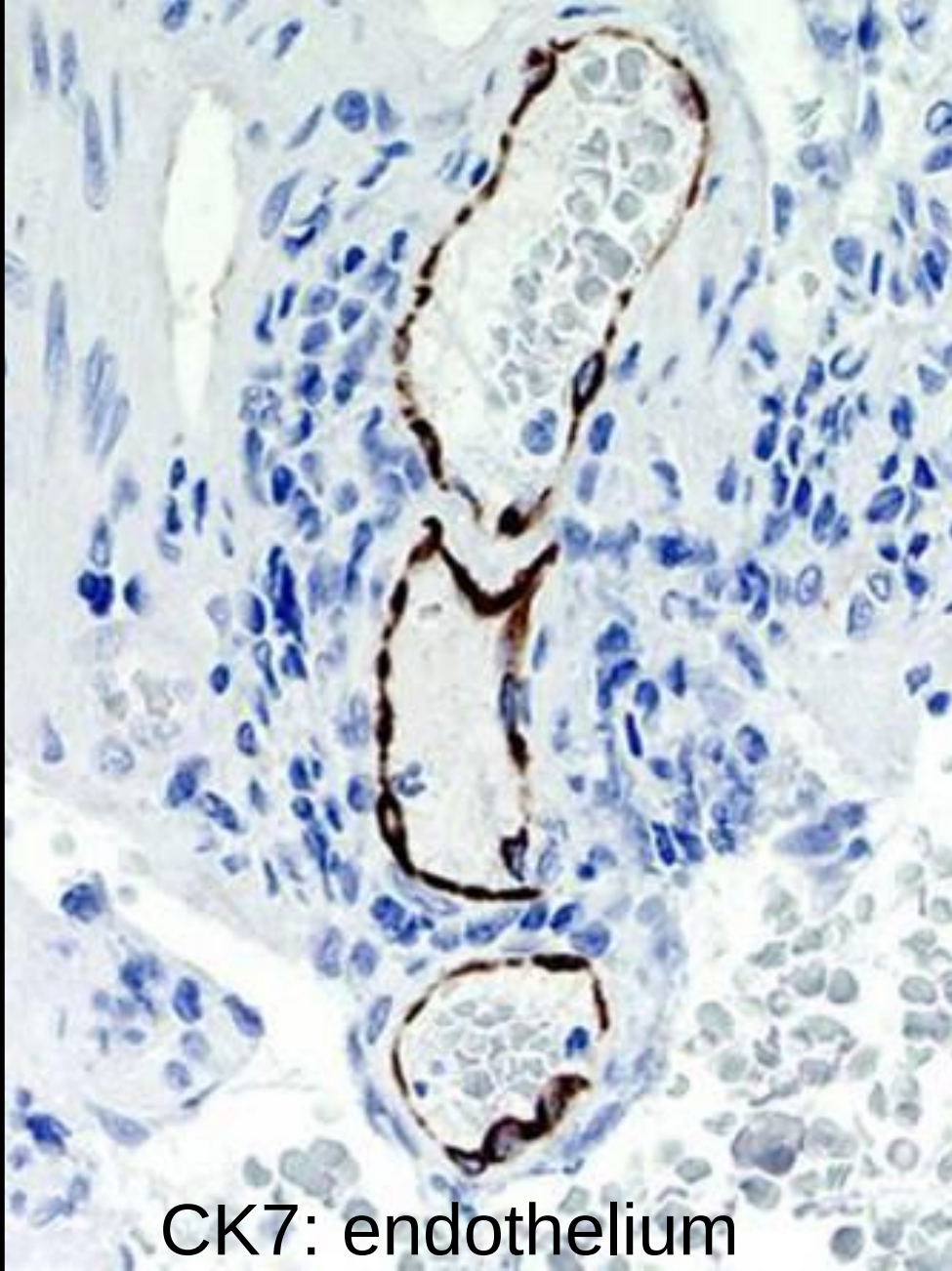


CK8: Pancreas

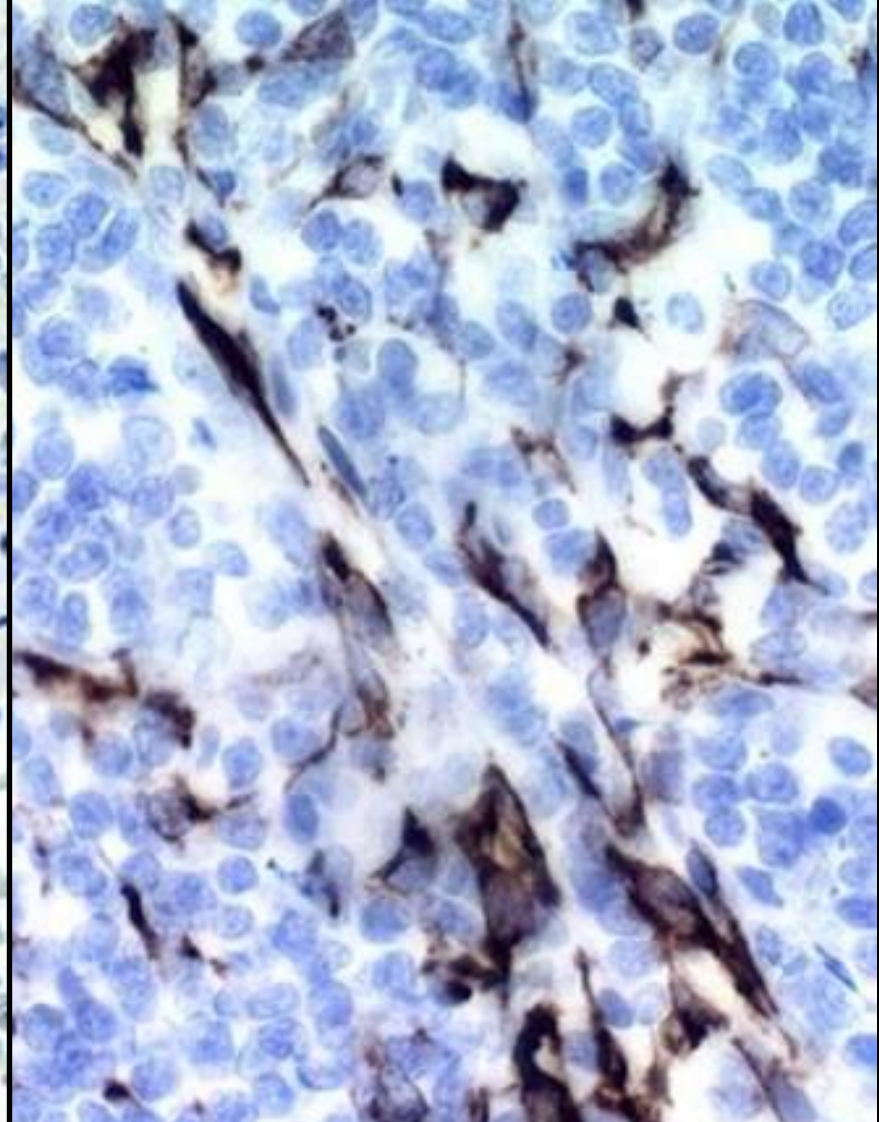
Cytokeratin types - mesenchymal cells

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous epithelia:										
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) ¹	-	-(+) ¹
Transit. epith.: superficial cells	-	-	-	-	-	-	+++	+++	++	+++
- intermed. / ³ basal cells	-	(+) ³	+++	(+++) ³	-	(++) ³	+++	+++	(+)	+++
Mesothelium	-	-	-	++	++	+	+++	+++	-	+++
Bronchus, breast, prost., cerv.:										
- basal/myoepithelial cells	-	-	-	+++	++	+++	++	-	-	-
- luminal cells	-	-	-	+	+	+	+++	+++	-	+++
Biliary/pancr. ducts, lung alv., endometr., renal collect. ducts	-	-	-	-	-	-	+++	+++	-	+++
⁴ Stomach (foveola), intestine	-	-	-	-	-	-	+++	(+) ⁴	+++	+++
Hepatocytes, pancr. acini, prox. renal tubules	-	-	-	-	-	-	-	-	-	+++
Endocrine cells (⁵ Merkel, ⁶ thyr.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - mesenchymal cells



CK7: endothelium



CK8: lymph node
fibroblastic reticulum cells

Cytokeratins in epithelial neoplasias

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epithelia (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma	-	-	-	-	-	-	-	-	-	-
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

Cytokeratins in squamous cell carcinoma

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous cell carcinoma	+	+	+	++	++	+	+	+	-	+
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epithelia (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma	-	-	-	-	-	-	-	+	-	++
Renal cell carcinoma	-	-	-	-	-	-	+	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

Cytokeratins in squamous cell carcinoma

esophagus

CK5

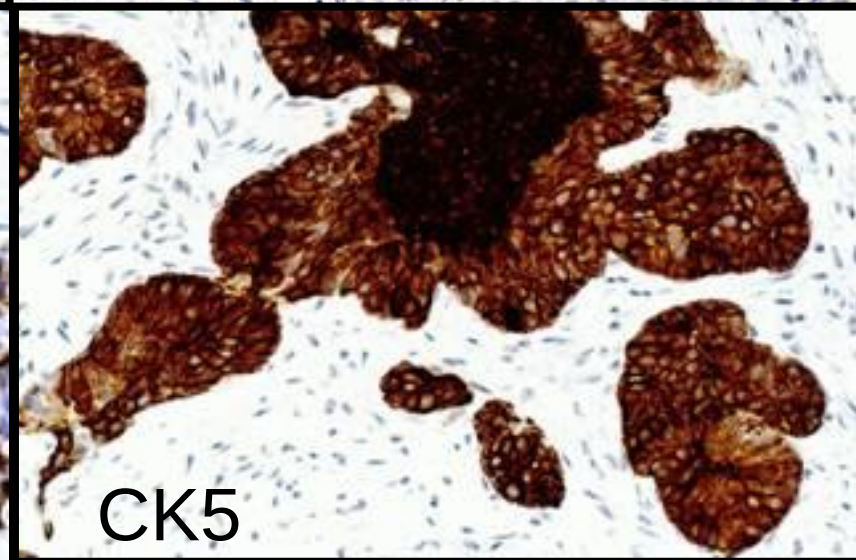
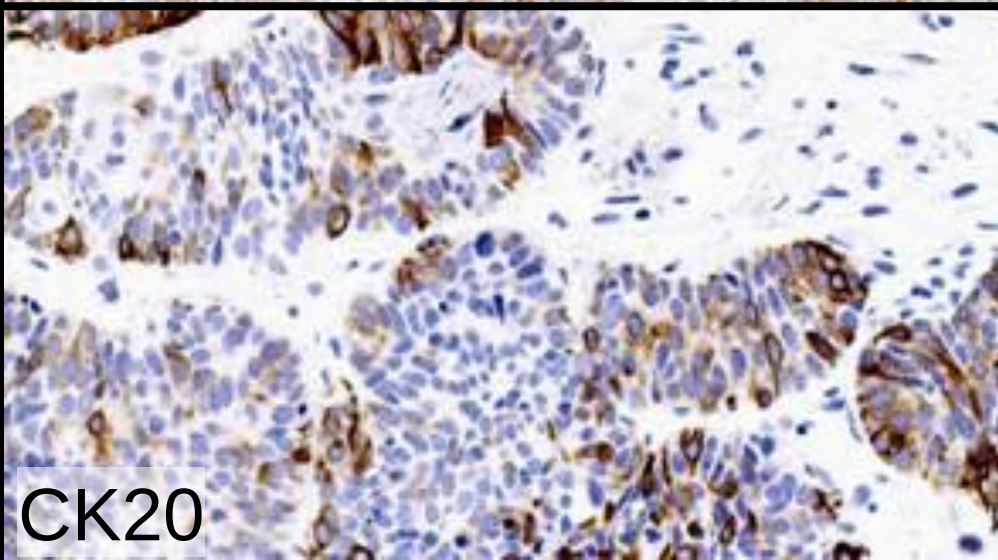
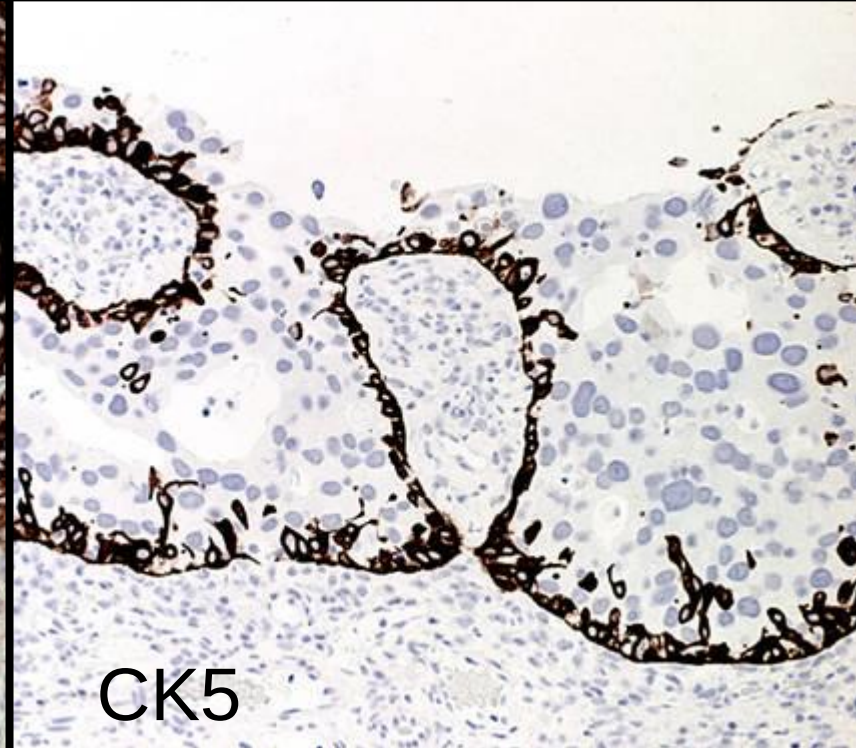
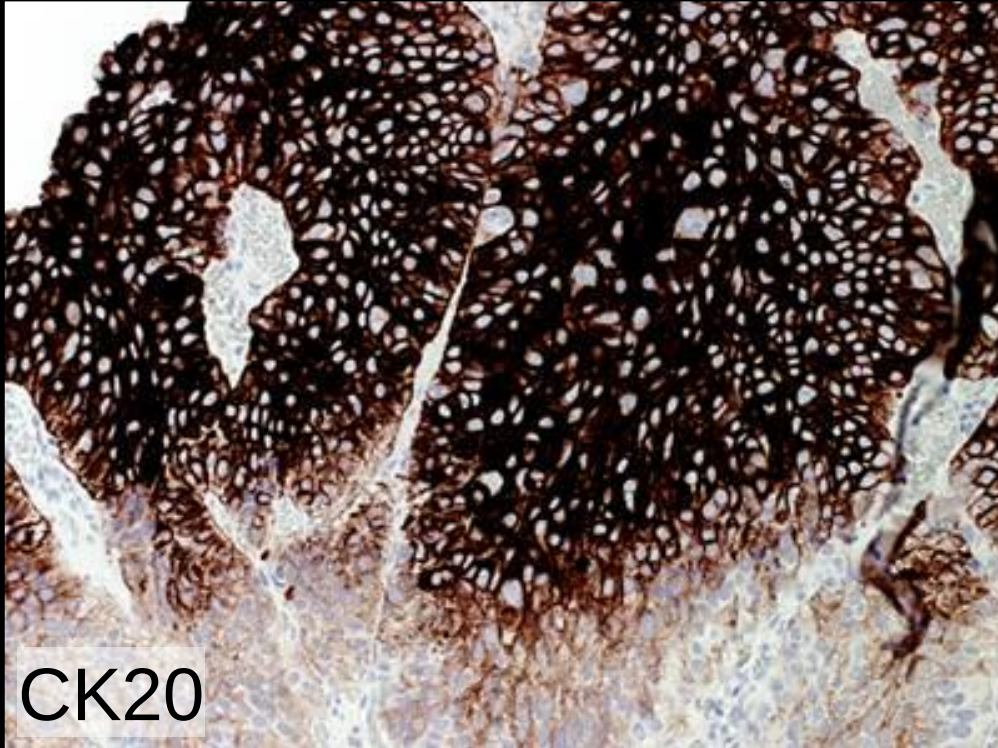


CK4

Cytokeratins in urothelial carcinoma

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous cell carcinoma	+	+	+	++	++	+	+	+	-	+
Transitional cell tumour	-	+	+	++	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epithelia (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma										
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

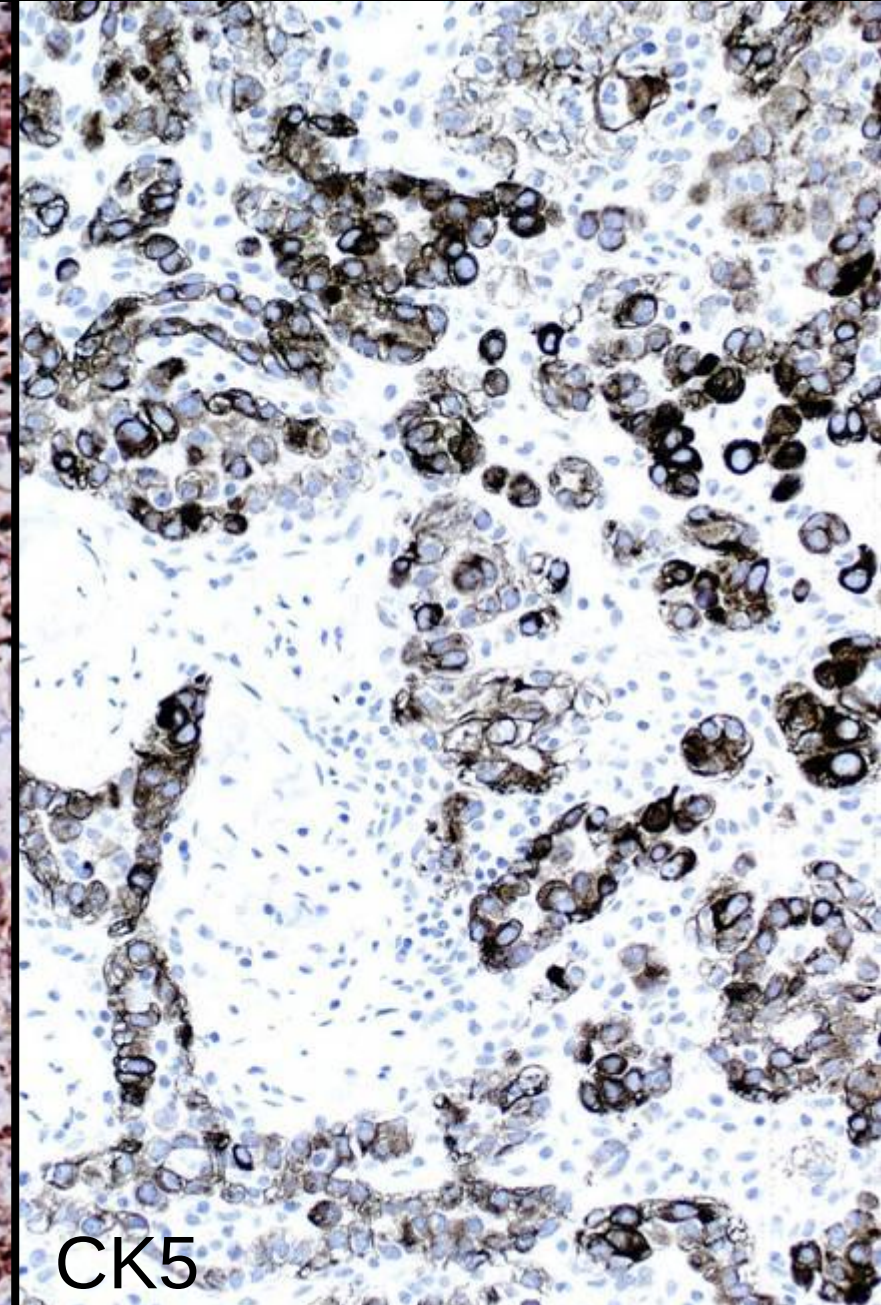
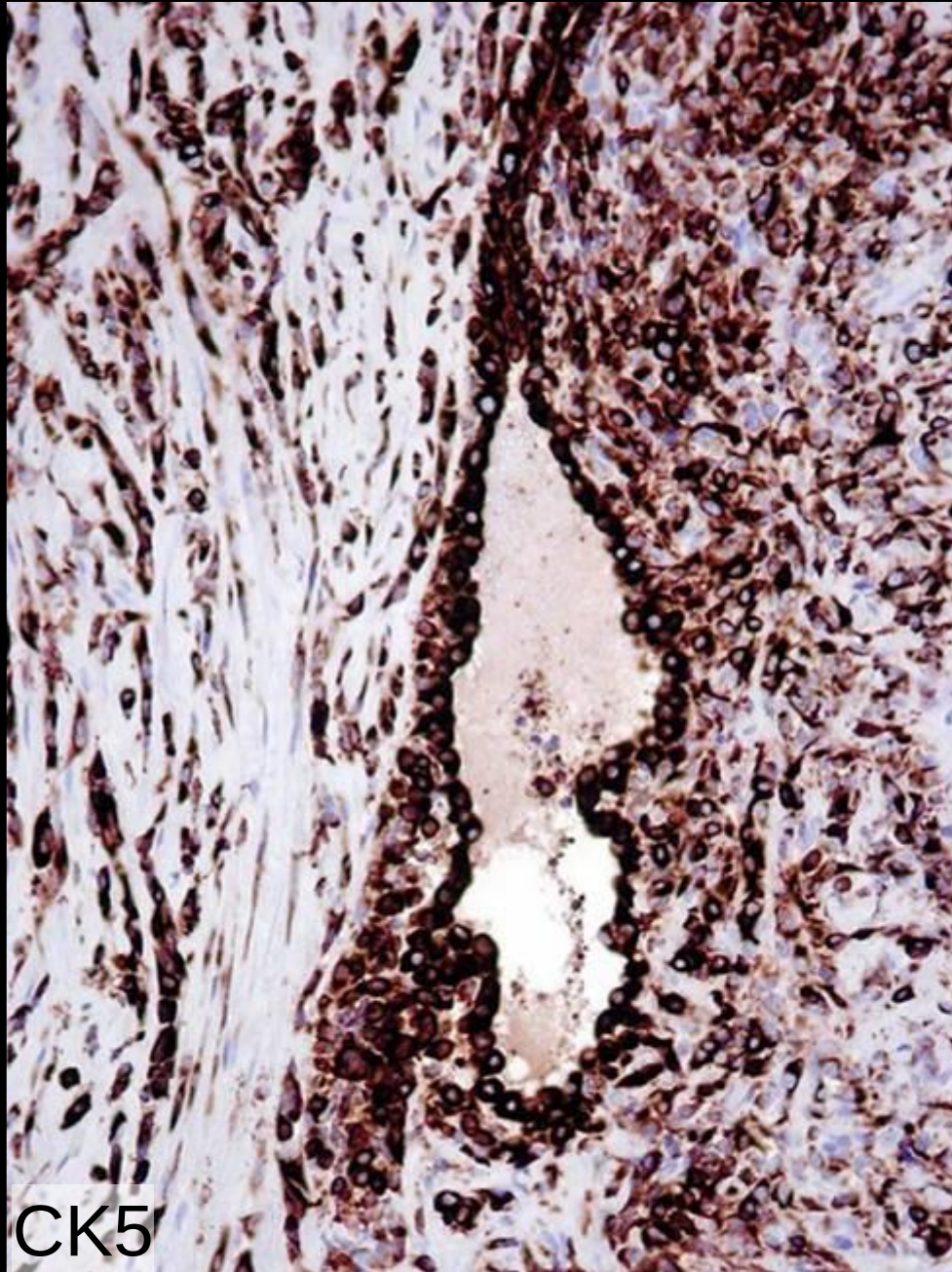
Cytokeratins in urothelial carcinoma



Cytokeratins in malignant mesothelioma

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epithelia (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma	-	-	-	-	-	-	-	-	-	-
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

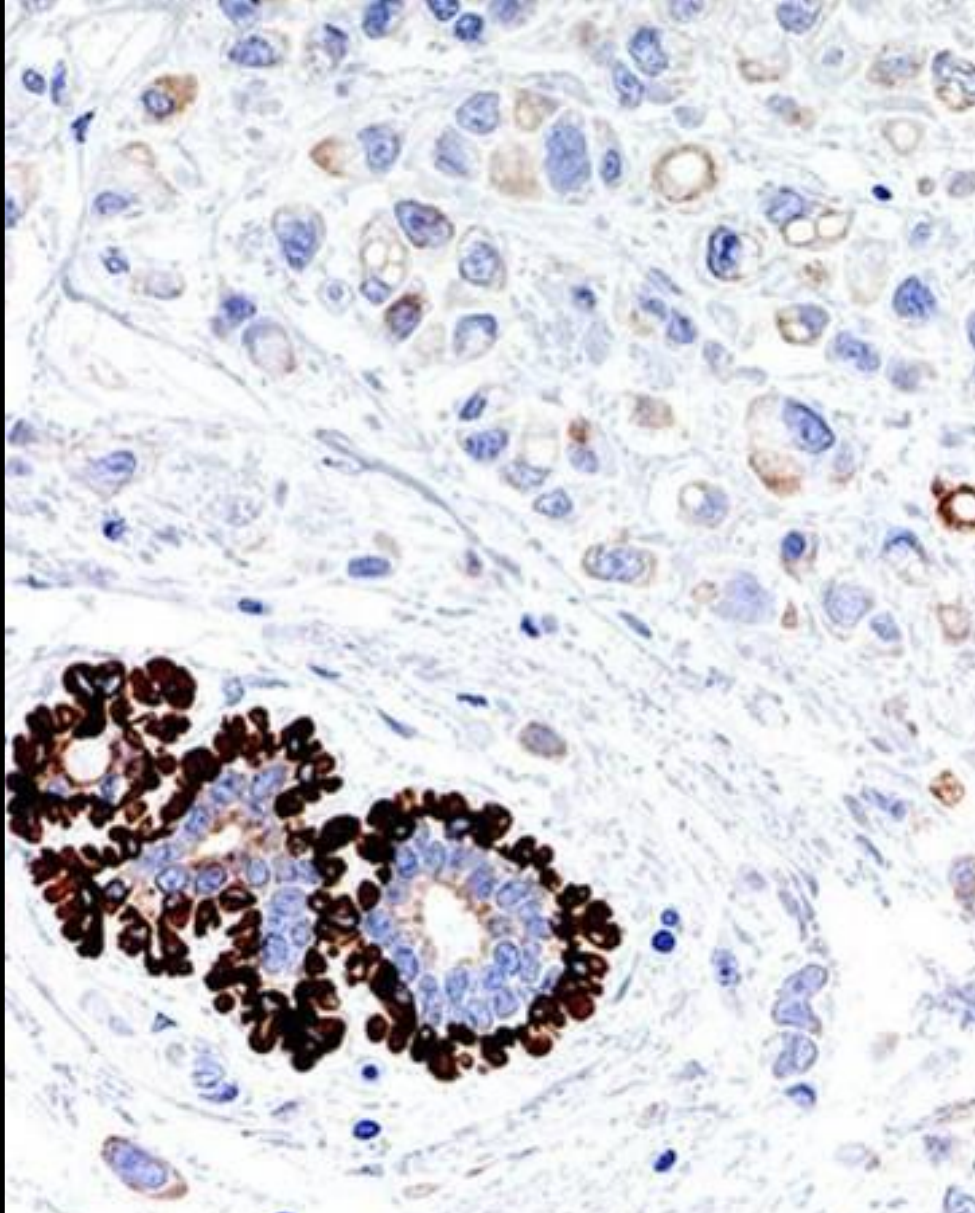
Cytokeratins in malignant mesothelioma



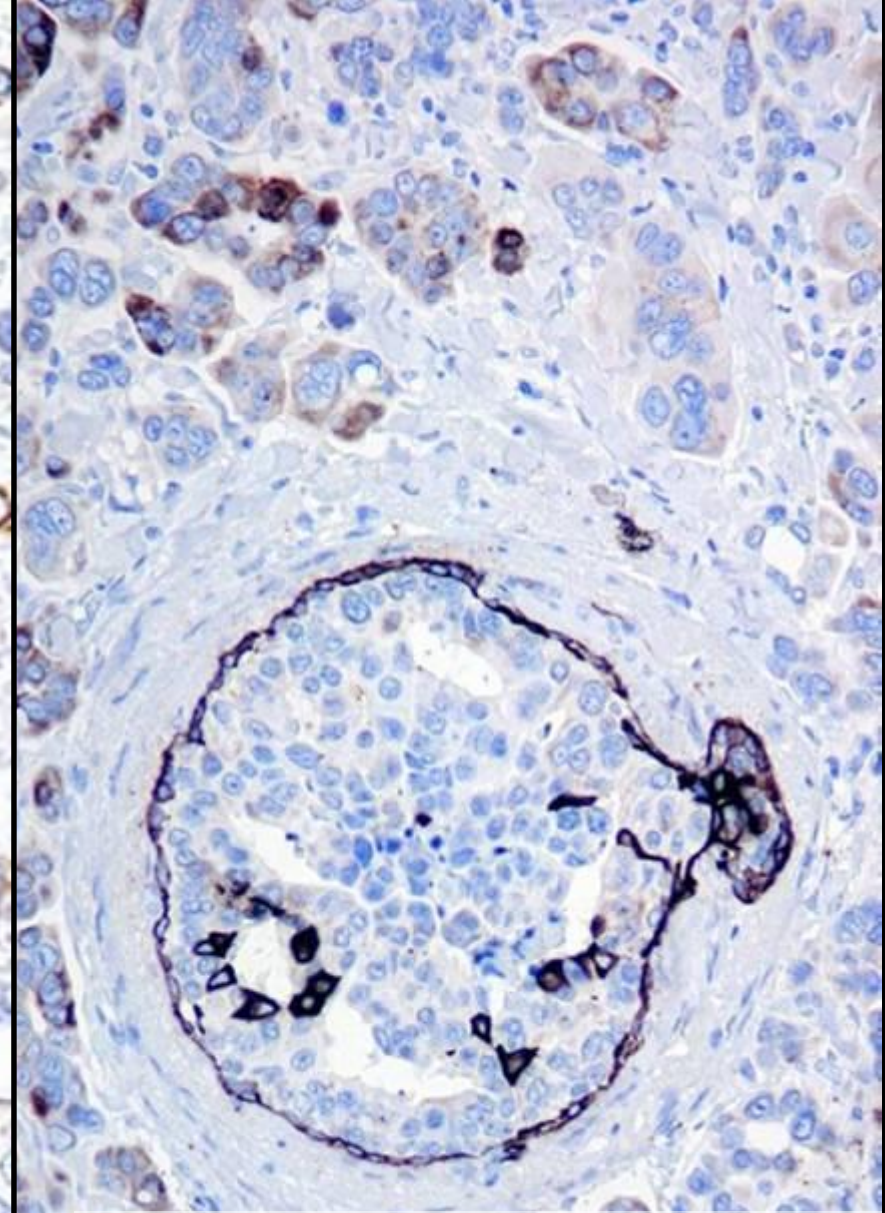
Cytokeratins in adenocarcinomas

Neutral/Basic (B, class II)	1	4		5				7		8
Acidic (A, class I)	10		13		14	17	19		20	18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epith. (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma										
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

Cytokeratins in adenocarcinomas

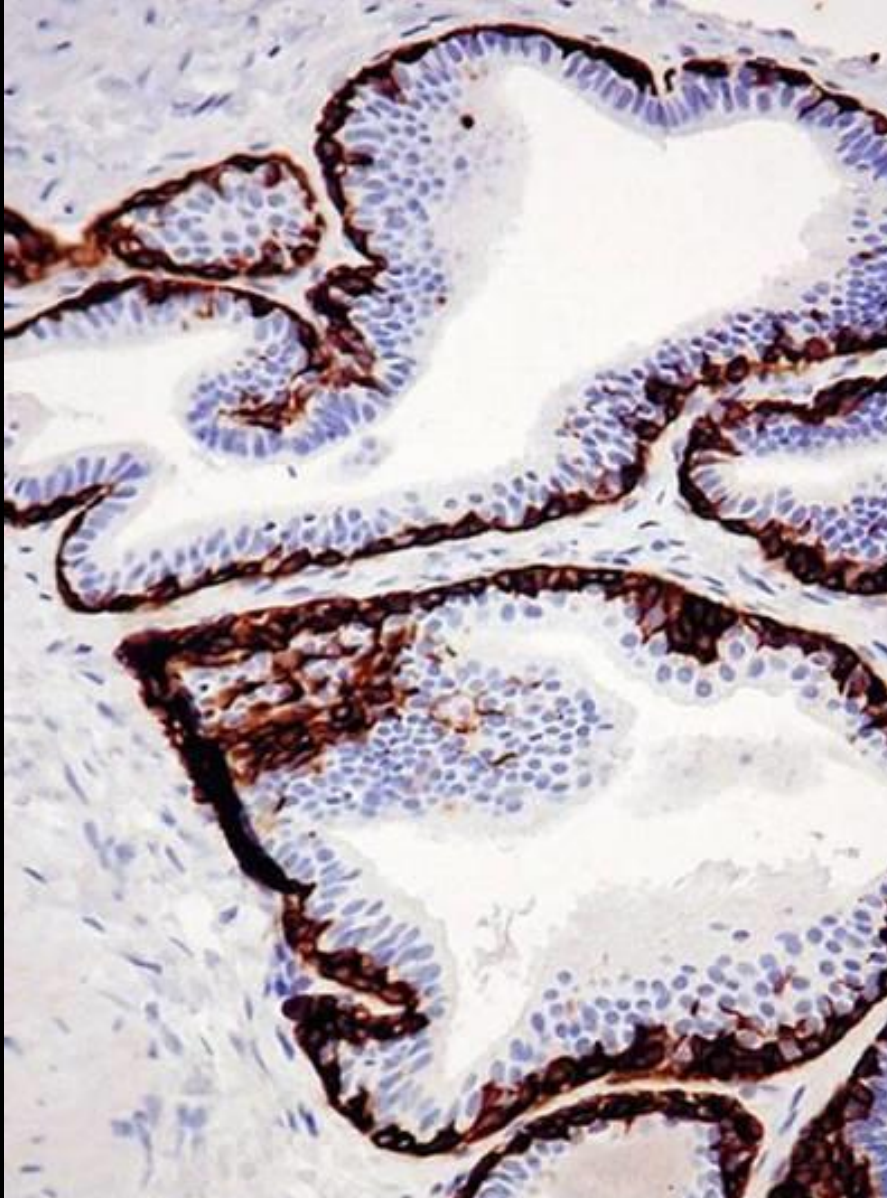


CK5: Breast lob. carcinoma

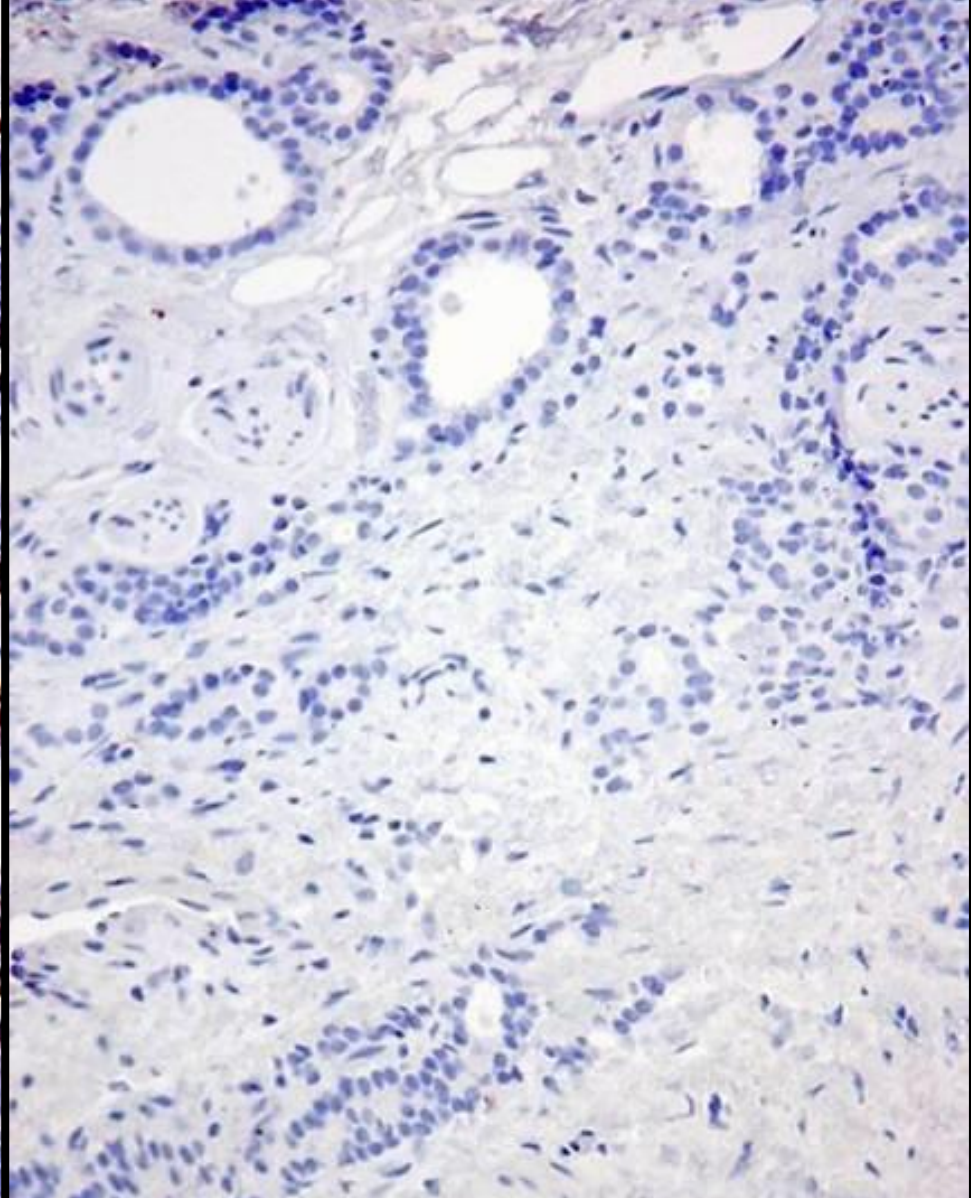


CK5: Breast duct. carc.

Cytokeratins in adenocarcinomas



CK5: Prostate hyperplasia

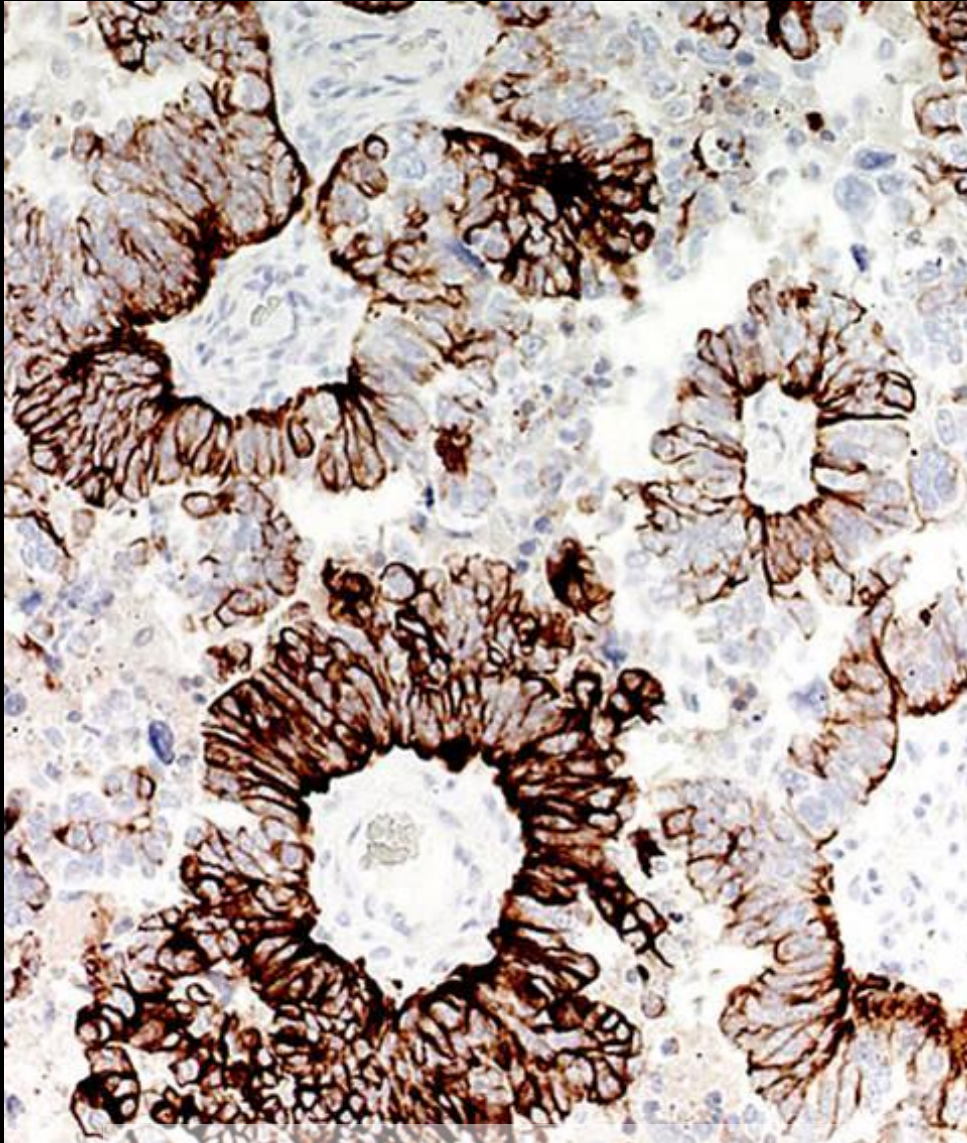


CK5: prostate adenocarc.

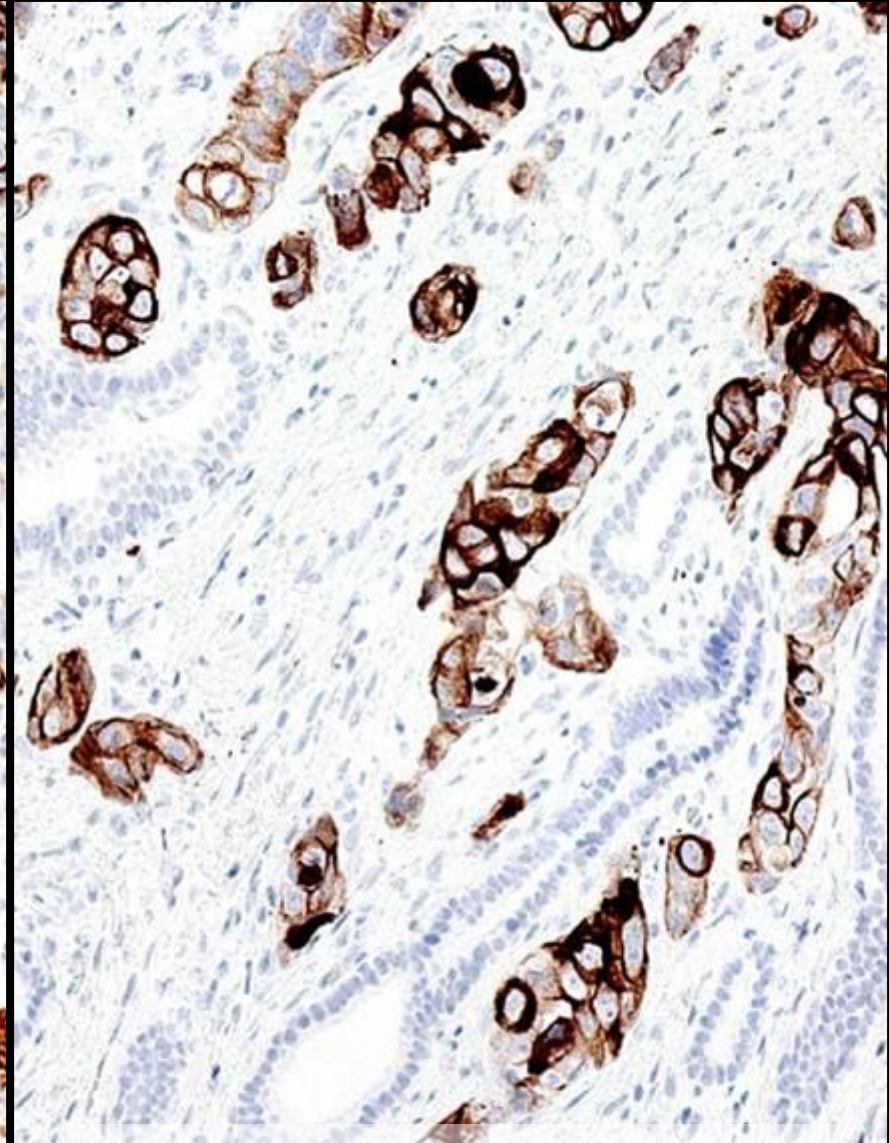
Cytokeratins in adenocarcinomas

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epith. (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+) !	(+) !	(+) !	++	++	(+) !	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma	-	-	-	-	-	-	-	+	-	++
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

Cytokeratins in adenocarcinomas



CK5: Serous ovarian carcinoma

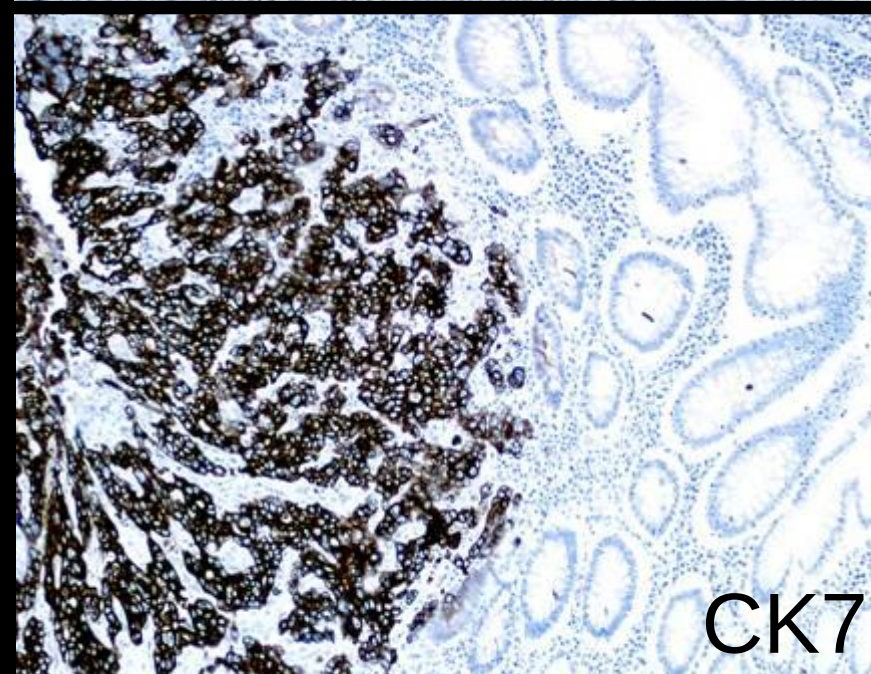
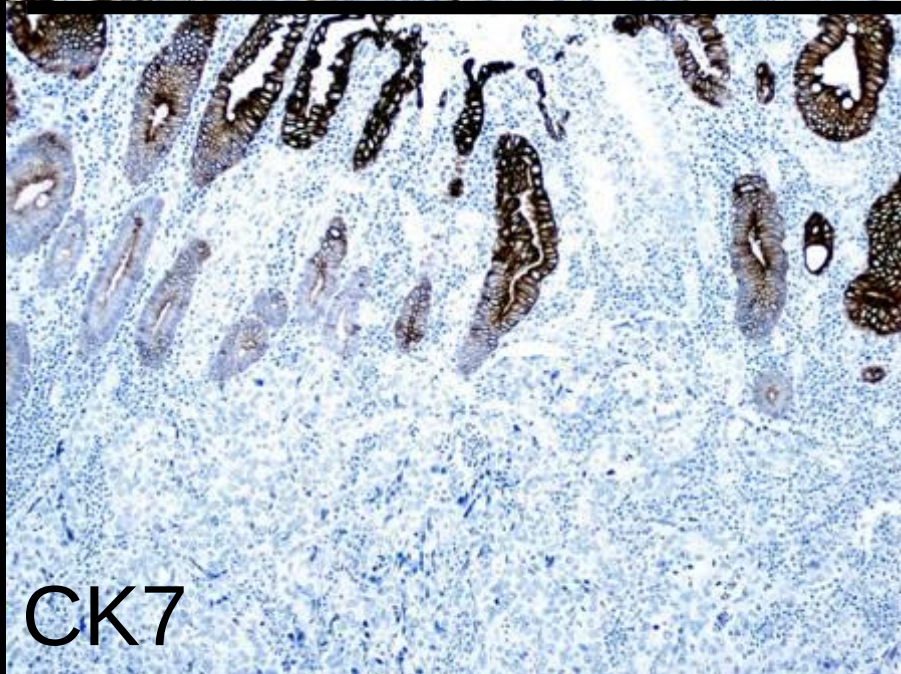
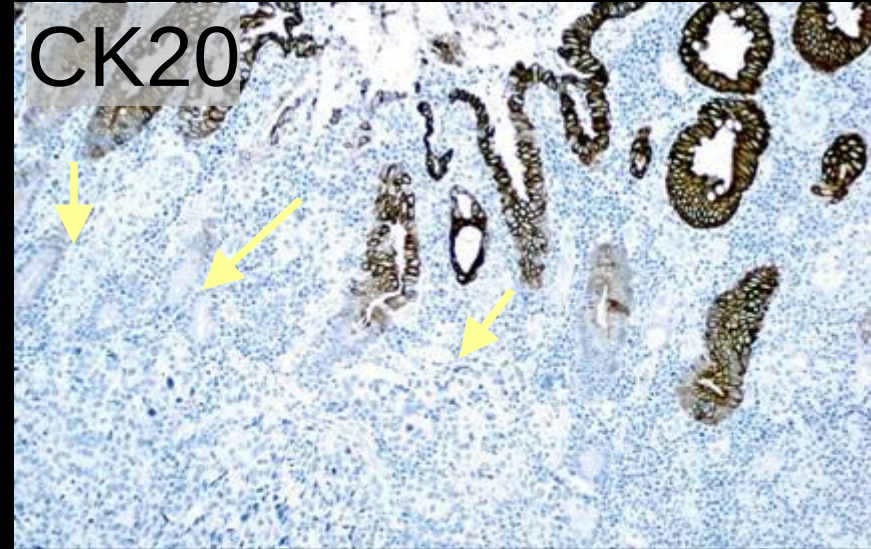
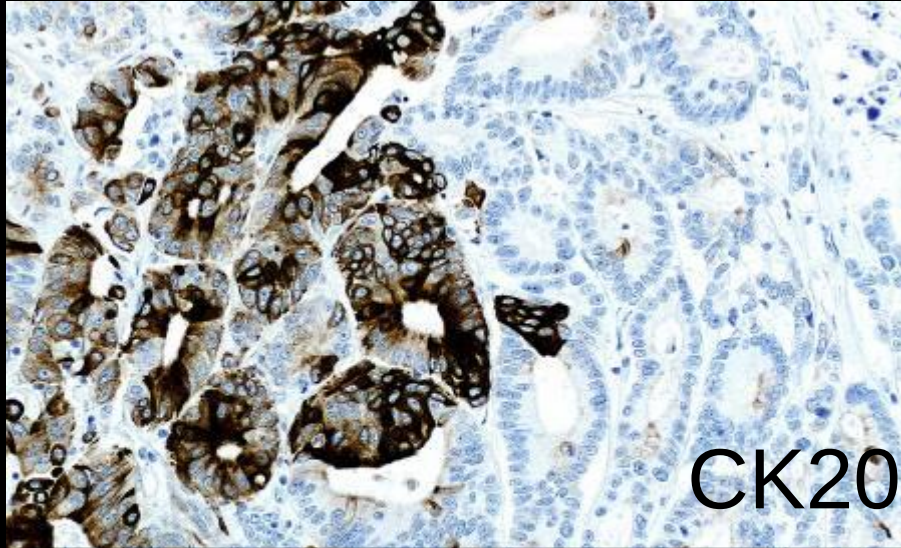


CK20: Gall bladder adenocarcinoma

Cytokeratins in adenocarcinomas

Neutral/Basic (B, class II) Acidic (A, class I)	1 10	4	13	5	14	17	19	7	20	8 18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epith. (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+ !	++	++
Hepatocellular carcinoma	-	-	-	-	-	-	-	+	-	++
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

Cytokeratins in adenocarcinomas



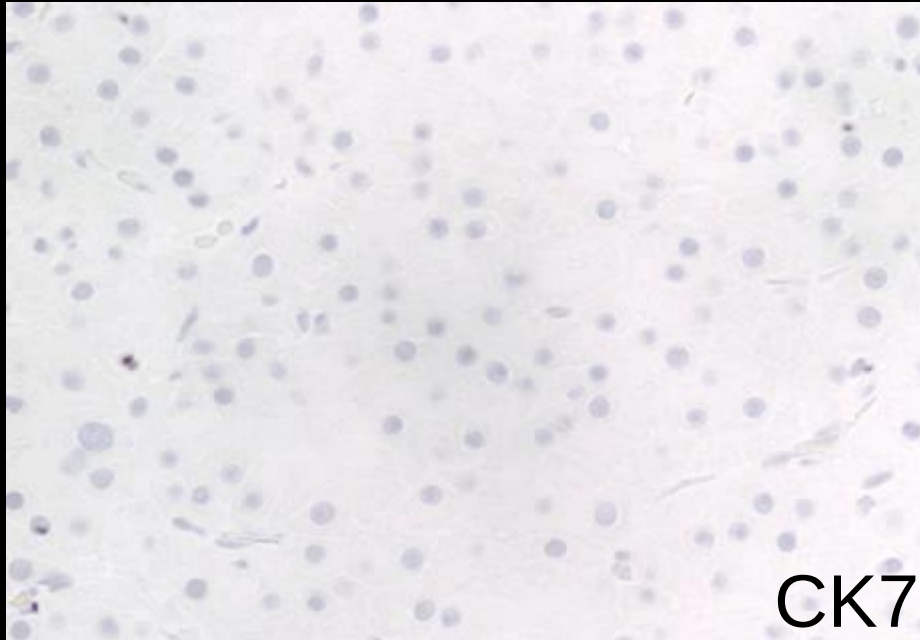
Colon: Typical

Colon: Deviant

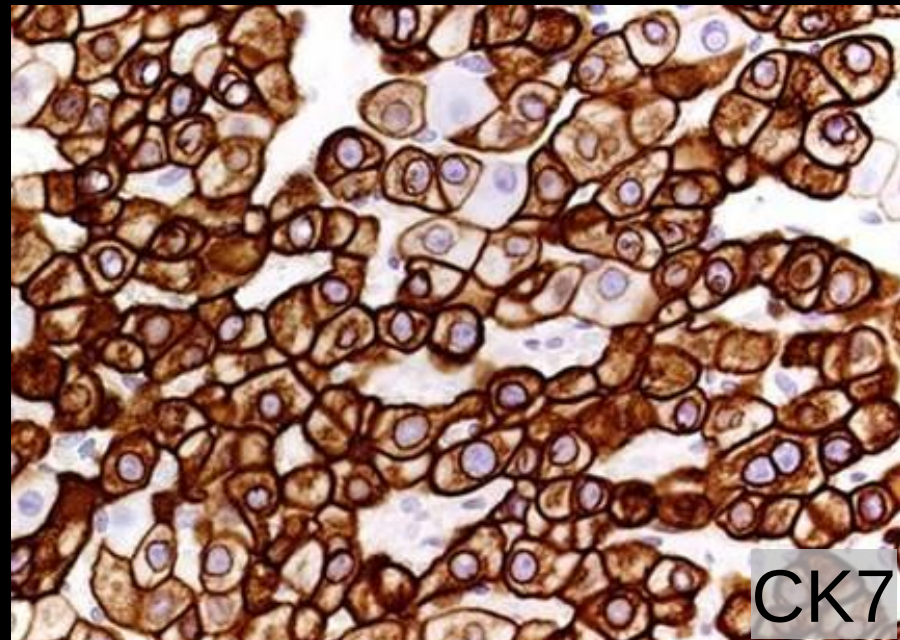
Cytokeratins in adenocarcinomas

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epith. (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma										
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocrine tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

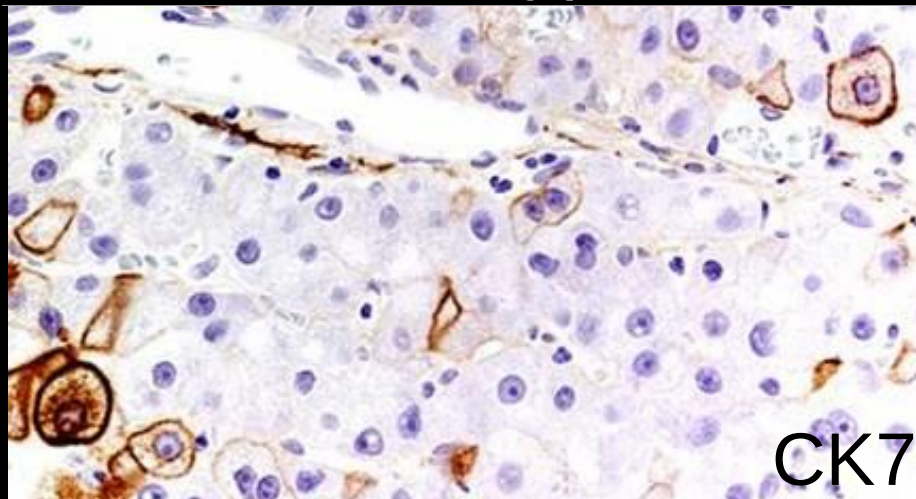
Cytokeratins in adenocarcinomas



HCC: typical



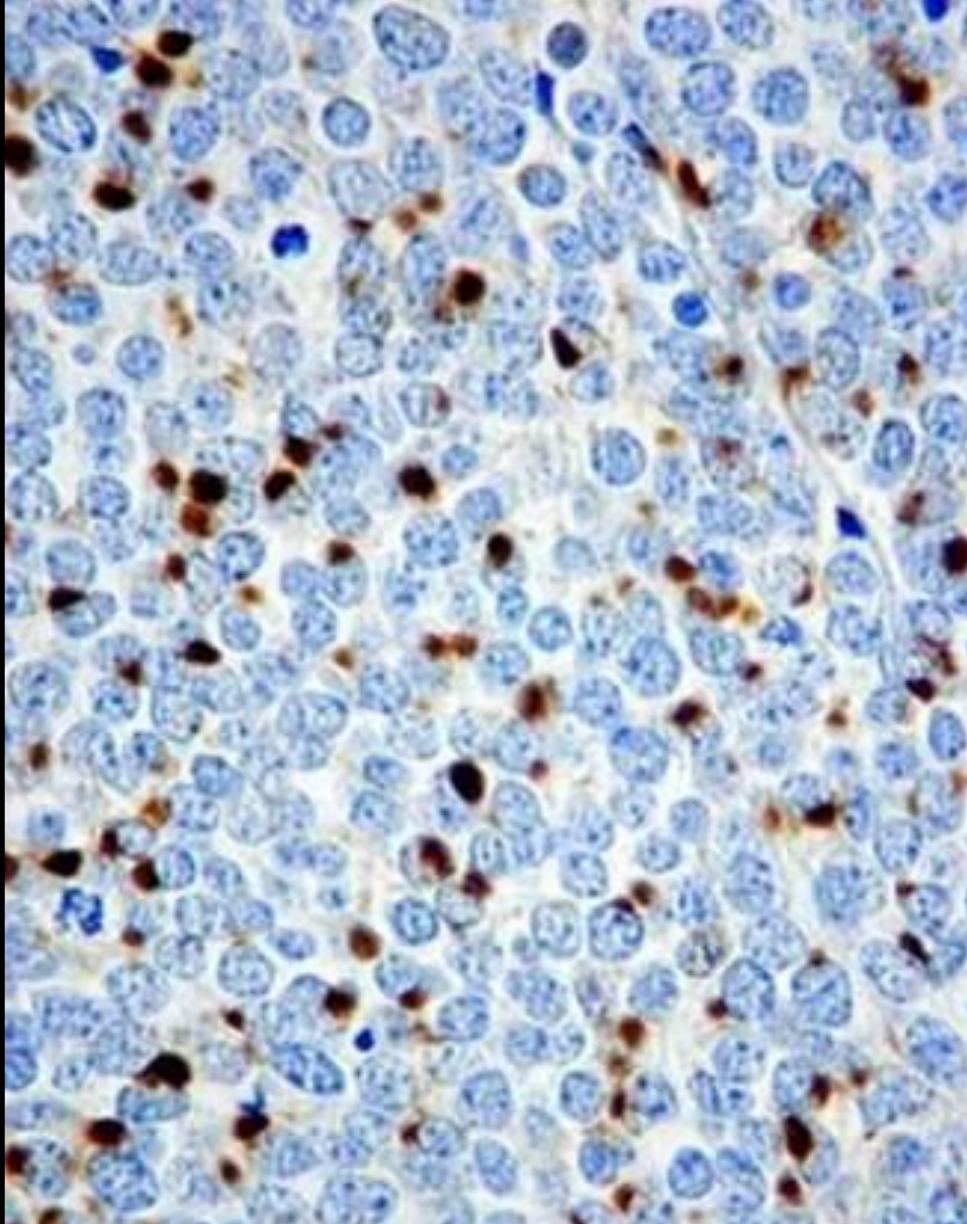
HCC: deviant



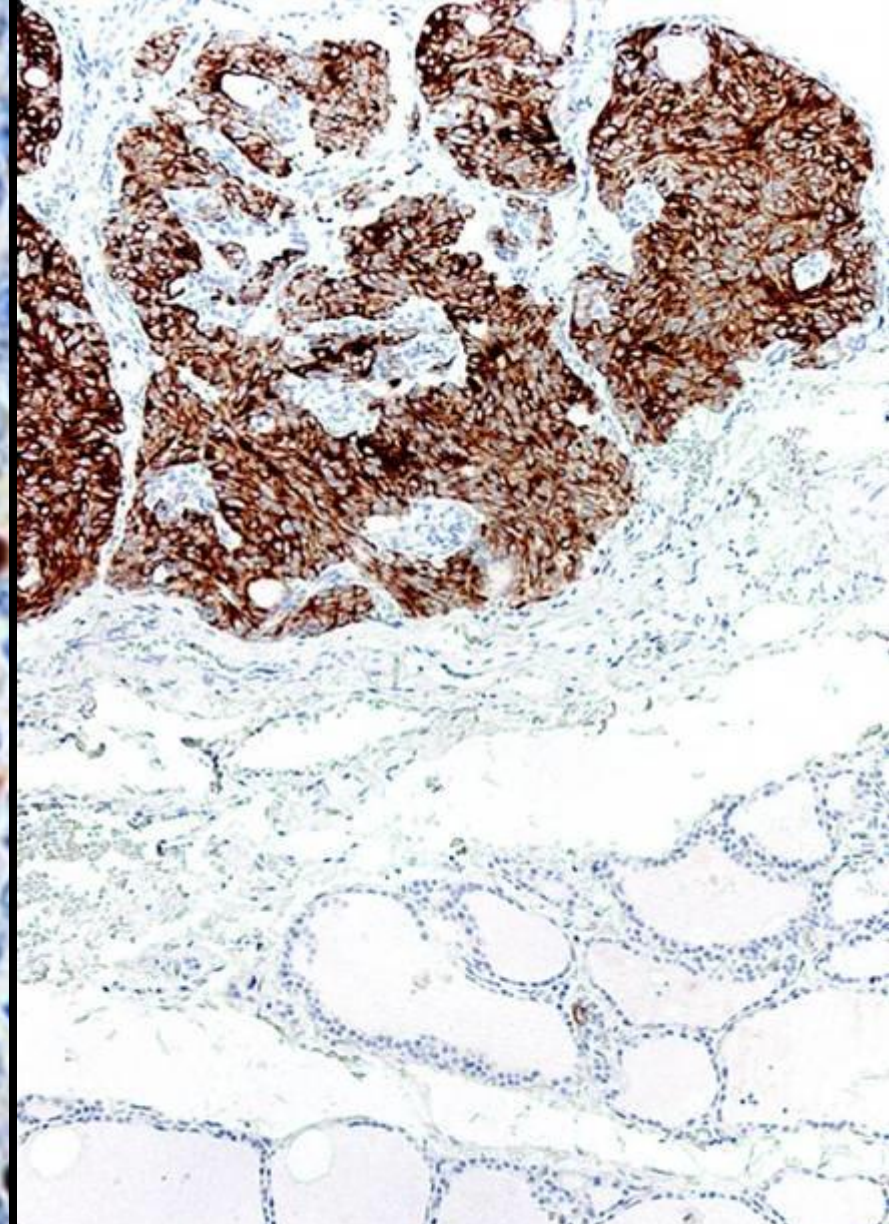
Cytokeratins in endocrine tumours

Neutral/Basic (B, class II)	1	4	13	5	14	17	19	7	20	8
Acidic (A, class I)	10									18
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epith. (bronch., breast, prost.)	-	-	-	(+)	(+)	(+)	++	++	-	++
Adenocarc.: biliary tract, pancr., endom., ovary	-	-	-	(+)	(+)	(+)	++	++	(+)	++
Adenocarc.: stomach	-	-	-	-	-	-	++	+	+	++
Adenocarc.: intestine	-	-	-	-	-	-	++	+	++	++
Hepatocellular carcinoma	-	-	-	-	-	-	-	+	-	++
Renal cell carcinoma	-	-	-	-	-	-	-	+	-	++
Endocr. tumours: carcinoids	-	-	-	-	-	-	+	+	-	++
- Merkel cell carcinoma	-	-	-	-	-	-	+	-	++	++
- Thyroid carcinoma	-	-	-	-	-	-	+	++	-	++

Cytokeratins in endocrine tumours



CK20: Merkel cell carc.



CK19: Thy. papill. carc.

Secondary panels for '**carcinoma**' identification/subclassification

Apart from cytokeratins and general markers (EpCAM, Cl4)

- "GI-markers" CEA, CDX2, CAD17, SMAD4
- "Fem.gen. tract markers" CA125, PAX8, WT1 (ER, p53)
- "Liver cell markers" AFP, Arginase, Glypican3, GlutSynt, Hepatocyte ag., canCD66a, canCD10
- Neuroendocrine markers Synaptophysin, Chromogranin
- "Breast markers" ER, GCDFP15, Mammaglob., GATA3
- "Lung & meso. markers" TTF-1, Napsin, p63/p40, Calretinin, Popoplanin,

Secondary panels for **carcinoma** identification/subclassification

- "Adrenal cortic.markers" Inhibin, Melan A
- Germinal cell markers SALL4, OCT3/4, PLAP, AFP, CD117, CD30
- Prostate & Urinary tract markers PSA, Prostein, AMACR, ERG
Uroplakin

“GI markers”

CDX2

CAD17

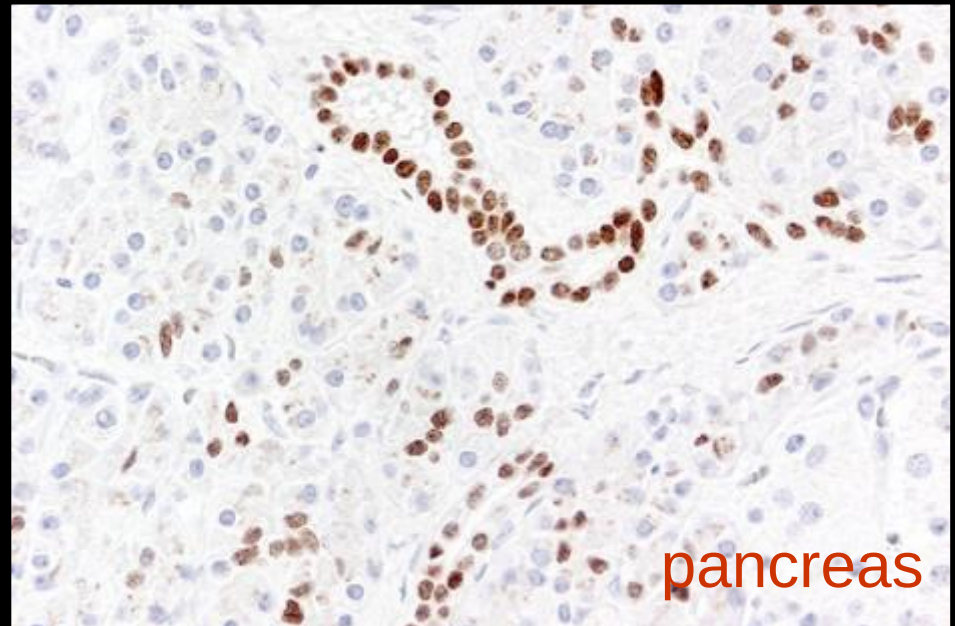
CEA

SMAD4

CDX-2 protein

Drosophila caudal related
homeobox gene 2 product:
Nuclear transcription factor
for intestinal differentiation

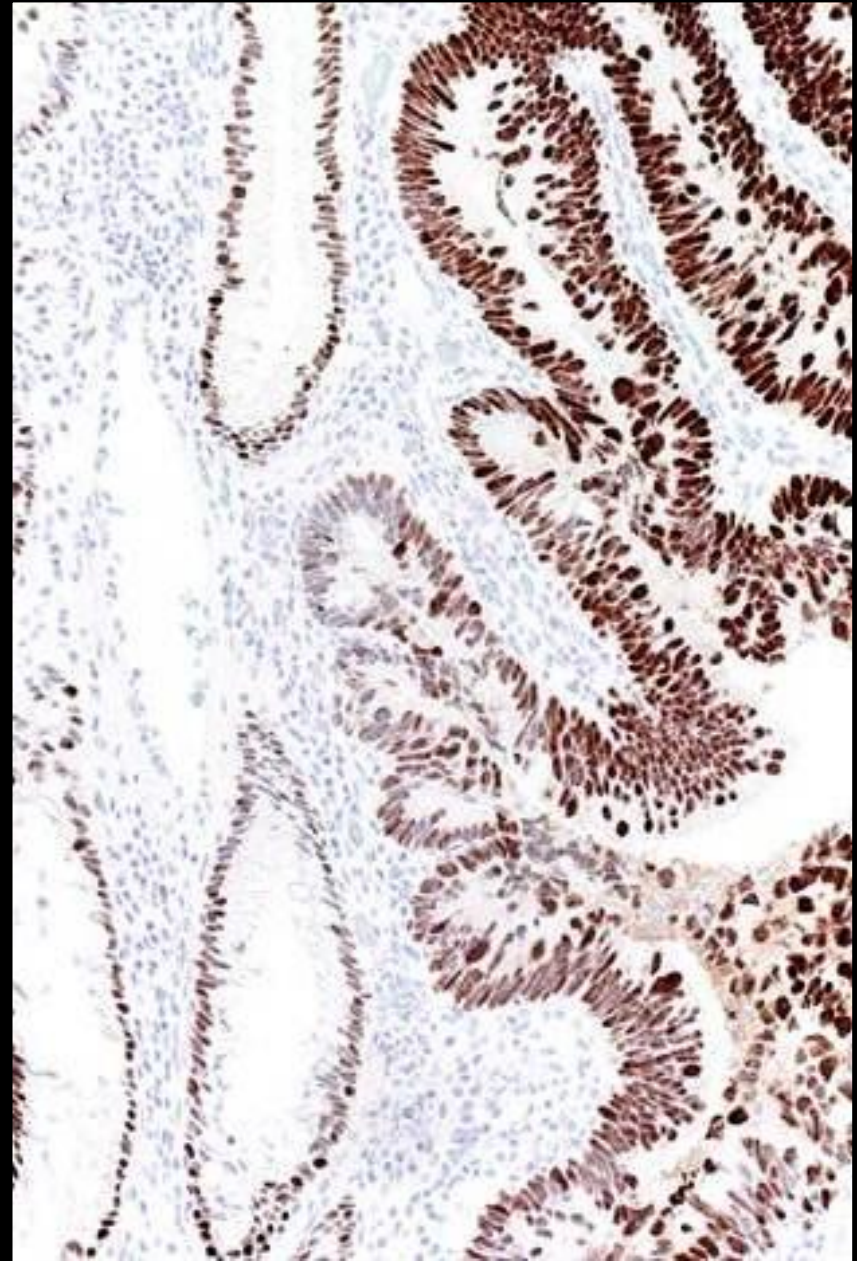
- Intestine
 - all cell types incl. endocrine
- Intestinal metaplasia
 - chronic gastritis
 - Barrett's esophagus
- Pancreas/bil.tract
 - heterogenous



CDX-2 protein in adenocarcinoma

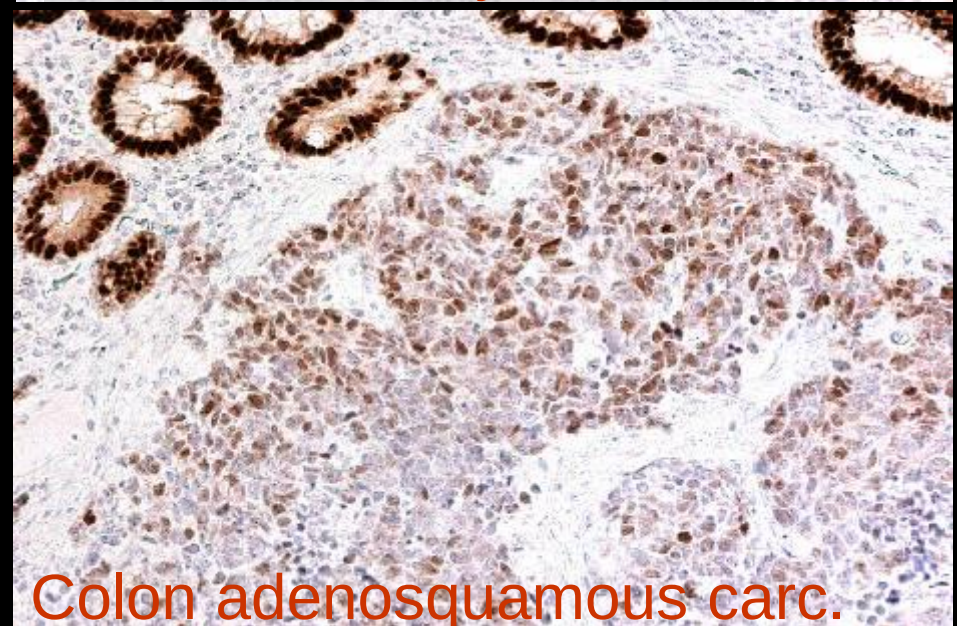
- Colorectum +(-)
- Mucinous ovar. +(-)
- Yolk sac tumour +
- Esoph./Stom. +/-
- Pancr./biliary -/+
- Lung -/+
- Prostate -(+)
- Urothelial -(+)
- Endometrioid -(+)

Colon adenocarcinoma

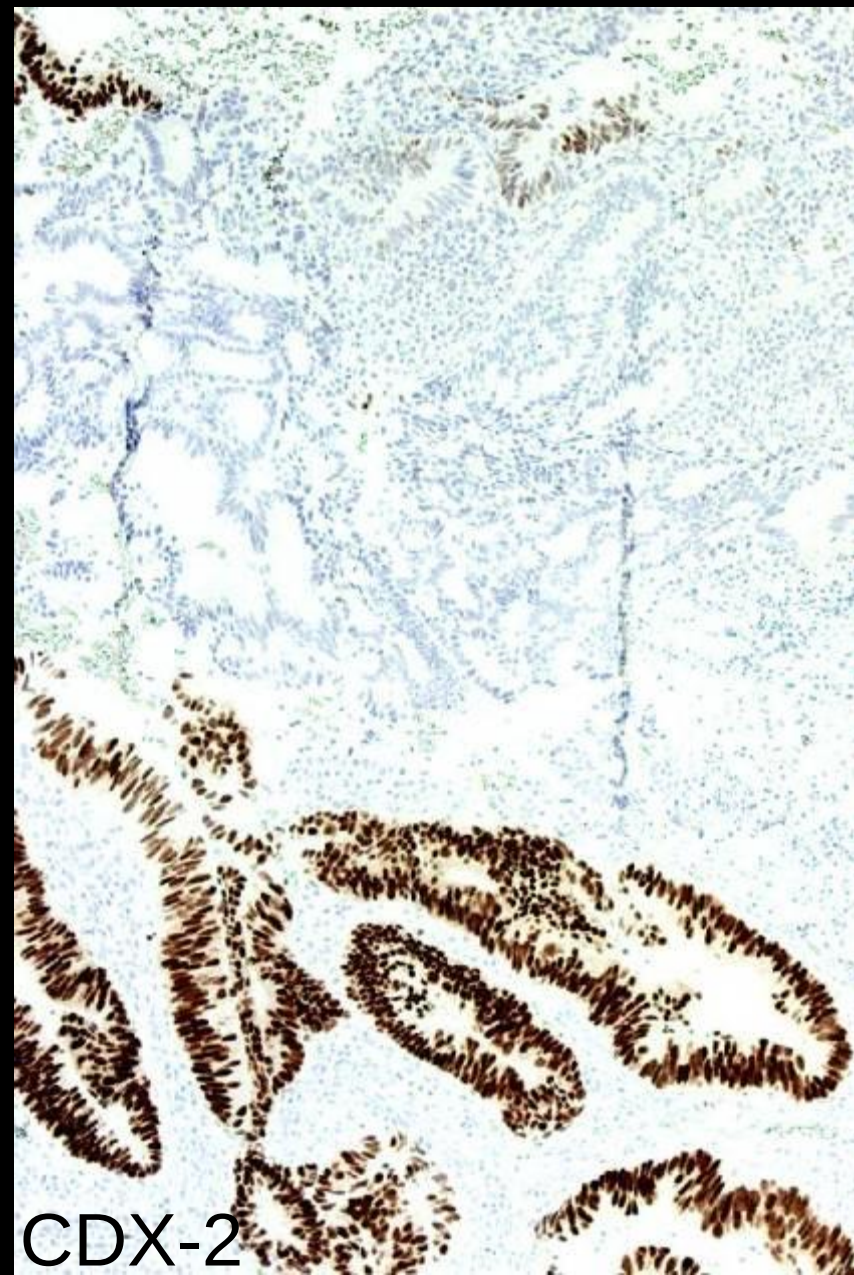
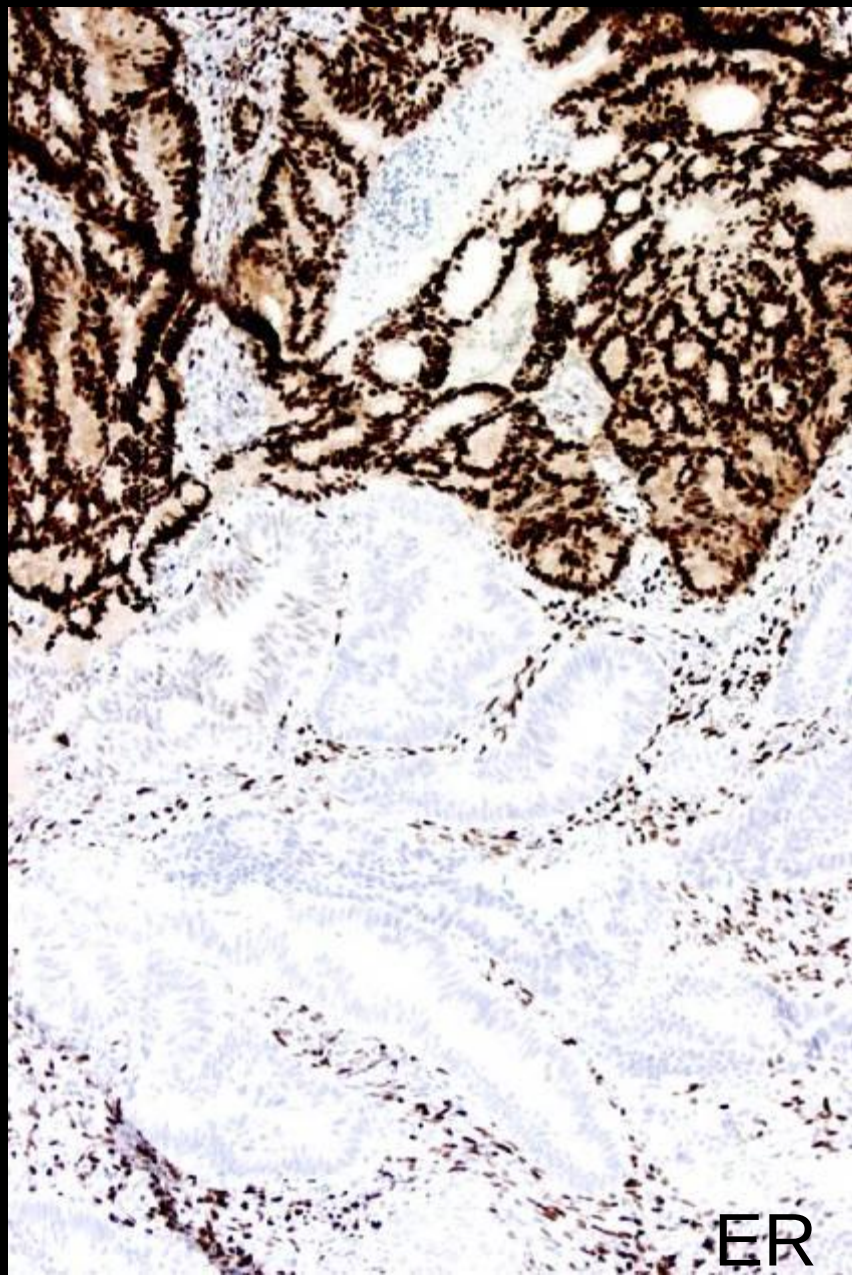


CDX-2 protein in adenocarcinoma

- Colorectum +(-)
- Mucinous ovar. +(-)
- Yolk sac tumour +
- Esoph./Stom. +/-
- Pancr./biliary -/+
- Lung -/+
- Prostate -(+)
- Urothelial -(+)
- Endometrioid -(+)

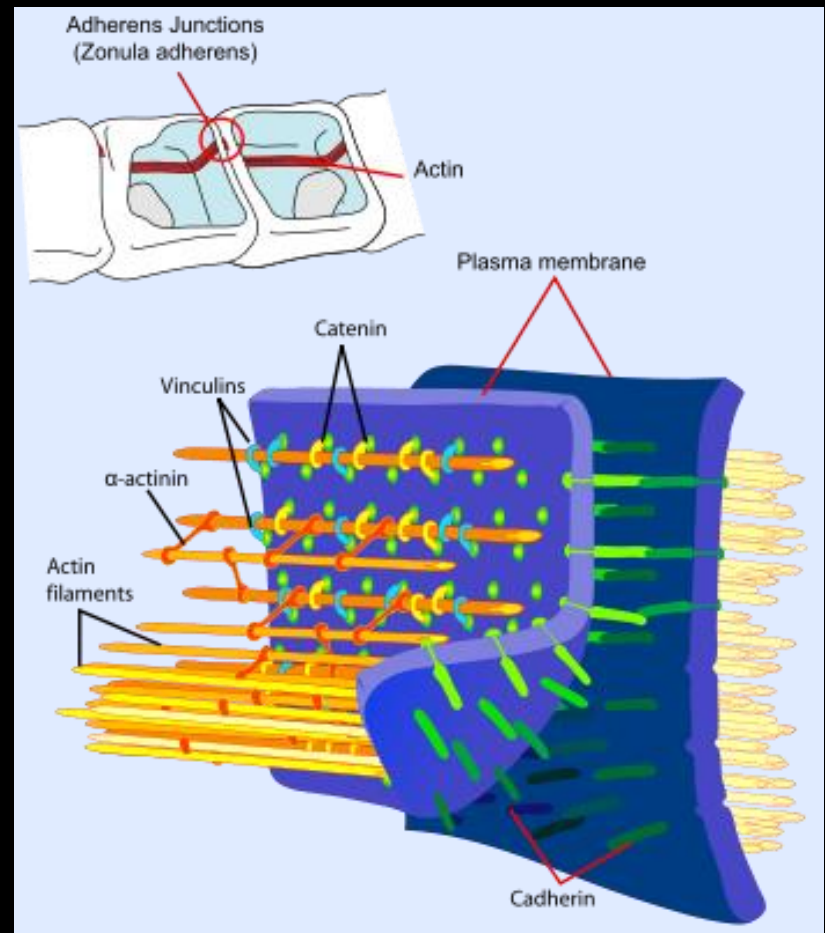


Endometrioid carcinoma: ER & CDX-2



Cadherin 17

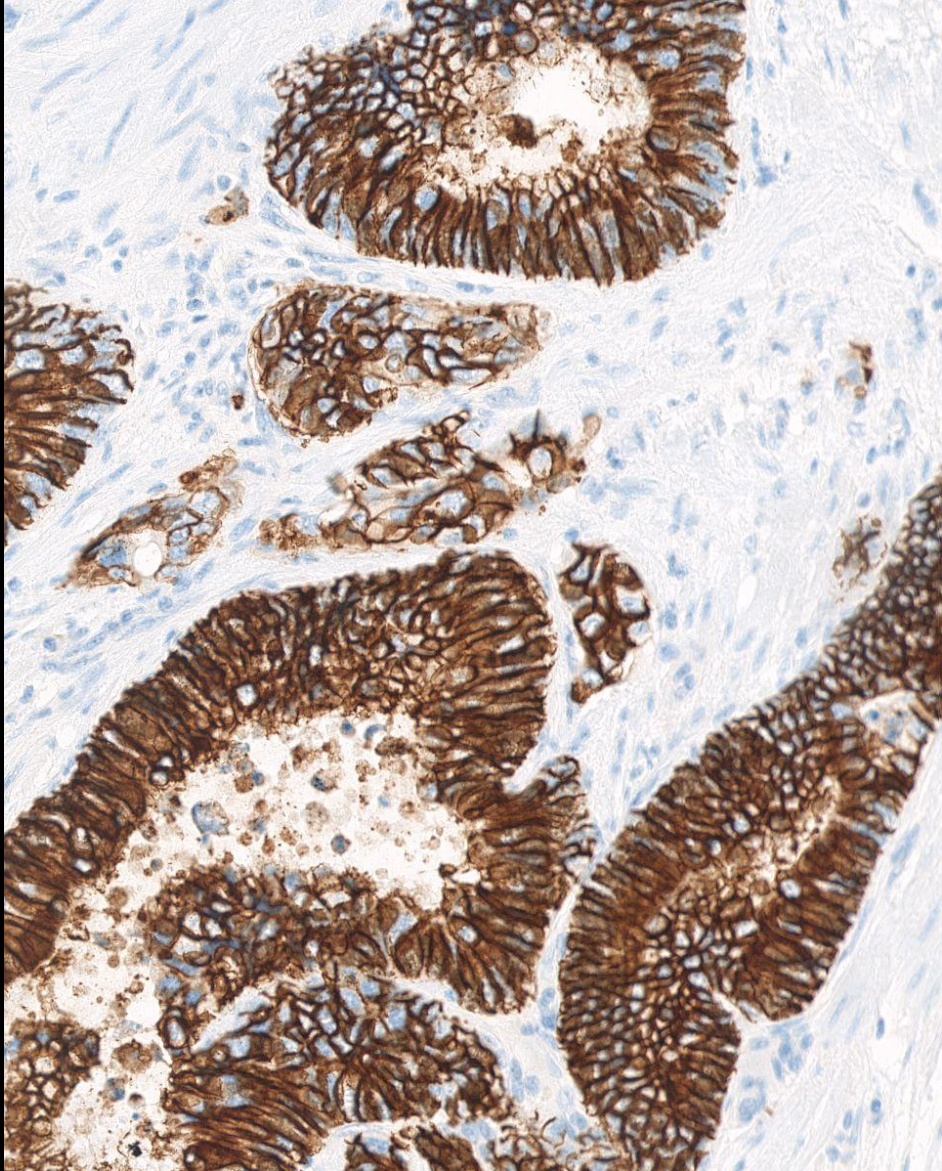
- Calcium dependent adhesion molecules
- CAD17 = Liver-Intestine (LI-) Cadherin
- Regulated by CDX2
- Intestine, pancreas



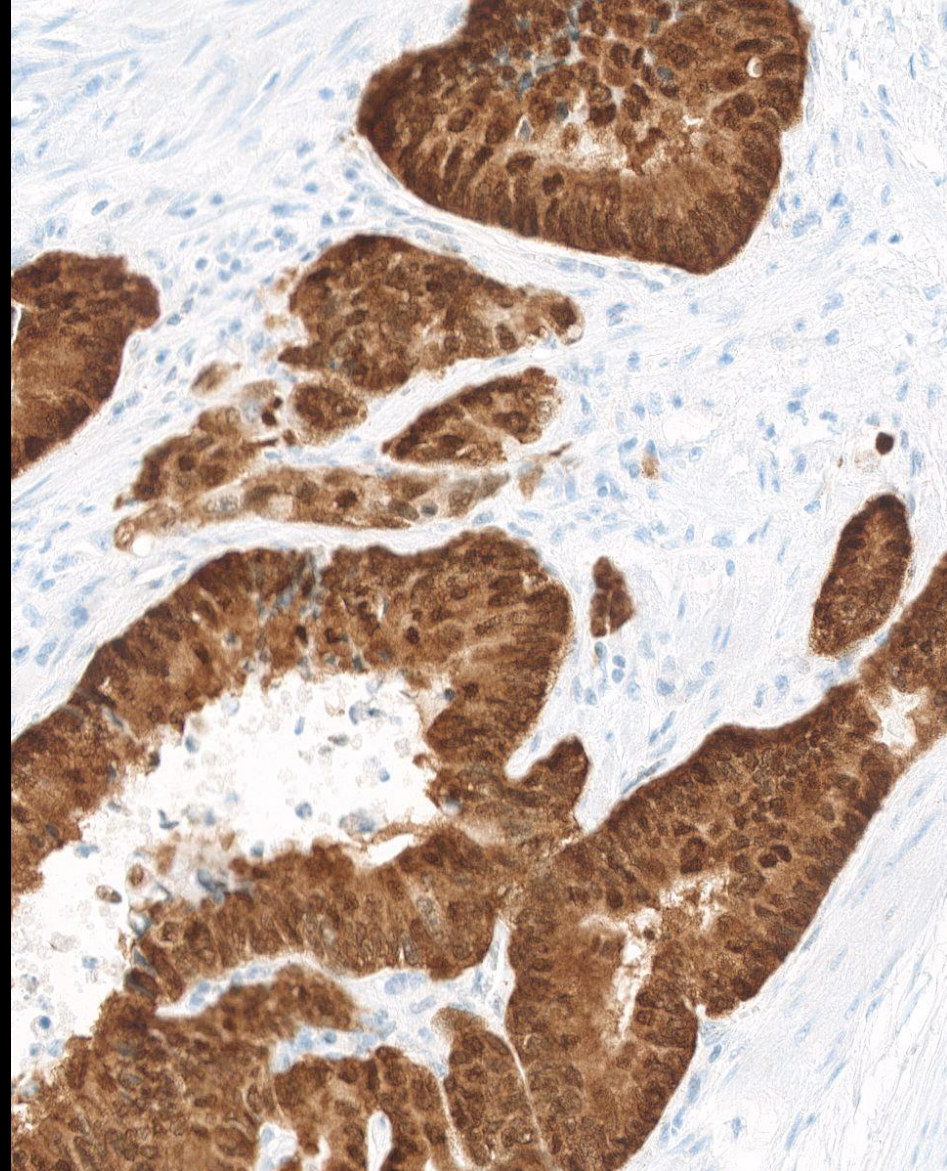
Cadherin 17

- Adenocarcinoma, colon + (100%)
- Adenocarc., esophagus, stomach, pancreas biliary tract +/-
- Adenocarc., lung, endometrium, ovary, breast -(+)
- Endocrine tumour, small intestine + (100%)
- Endocrine tumour, lung, pancreas. -/+
- Squamous cell carcinoma. -(+)

CAD17 and CDX2 – Colon adenocarcinoma

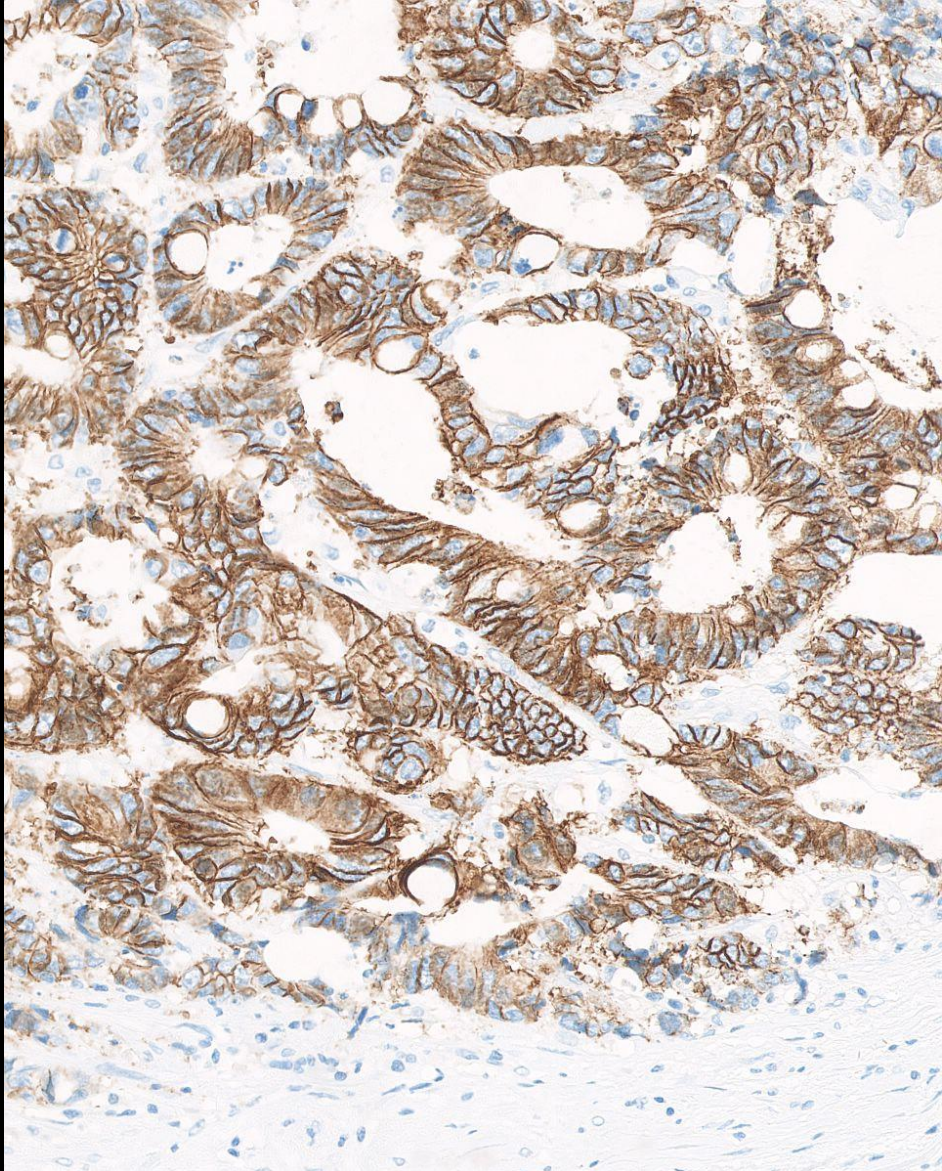


Cadherin 17: rmAb SP183, CM, 1:50,
CC1M/16M/UV

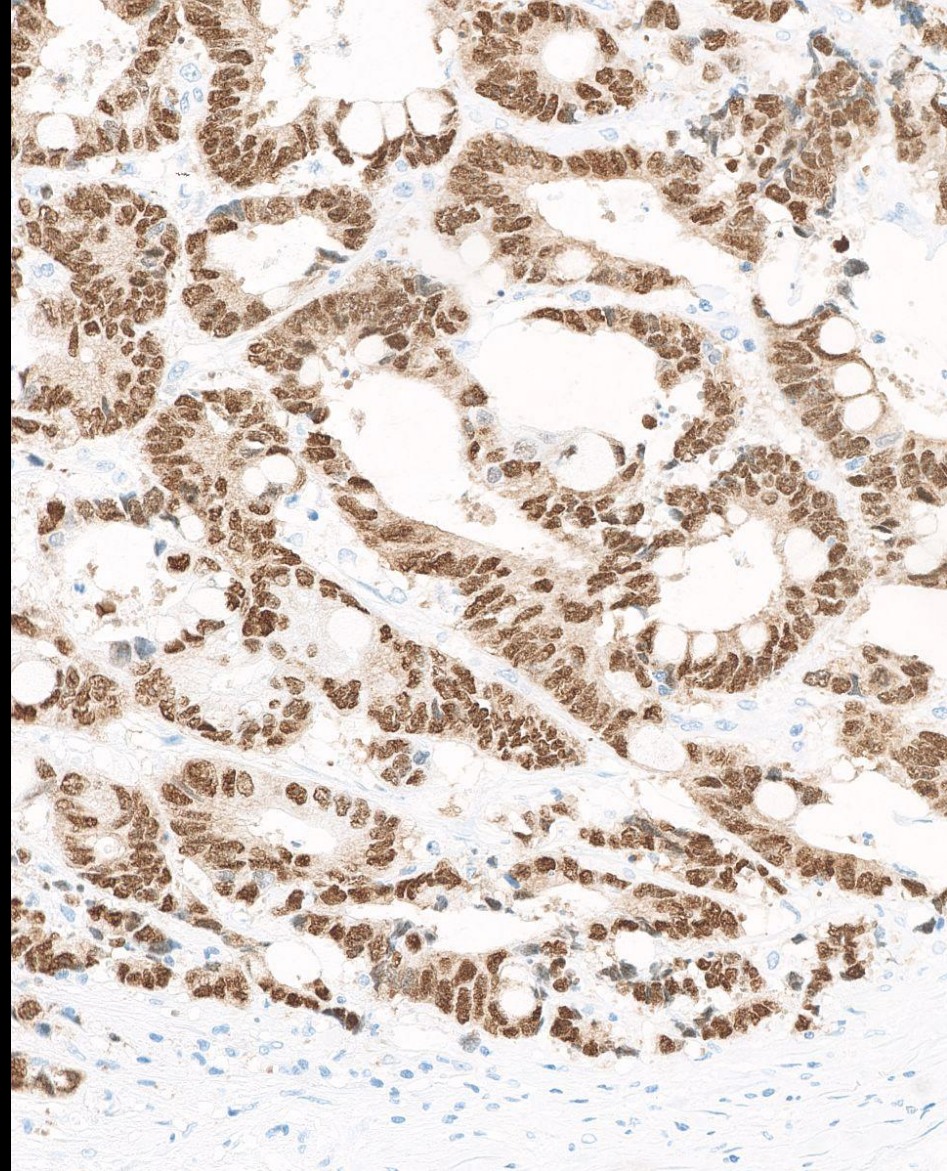


CDX2:
rmAb EPR2764Y, CM

CAD17 and CDX2 – Colon adenocarcinoma

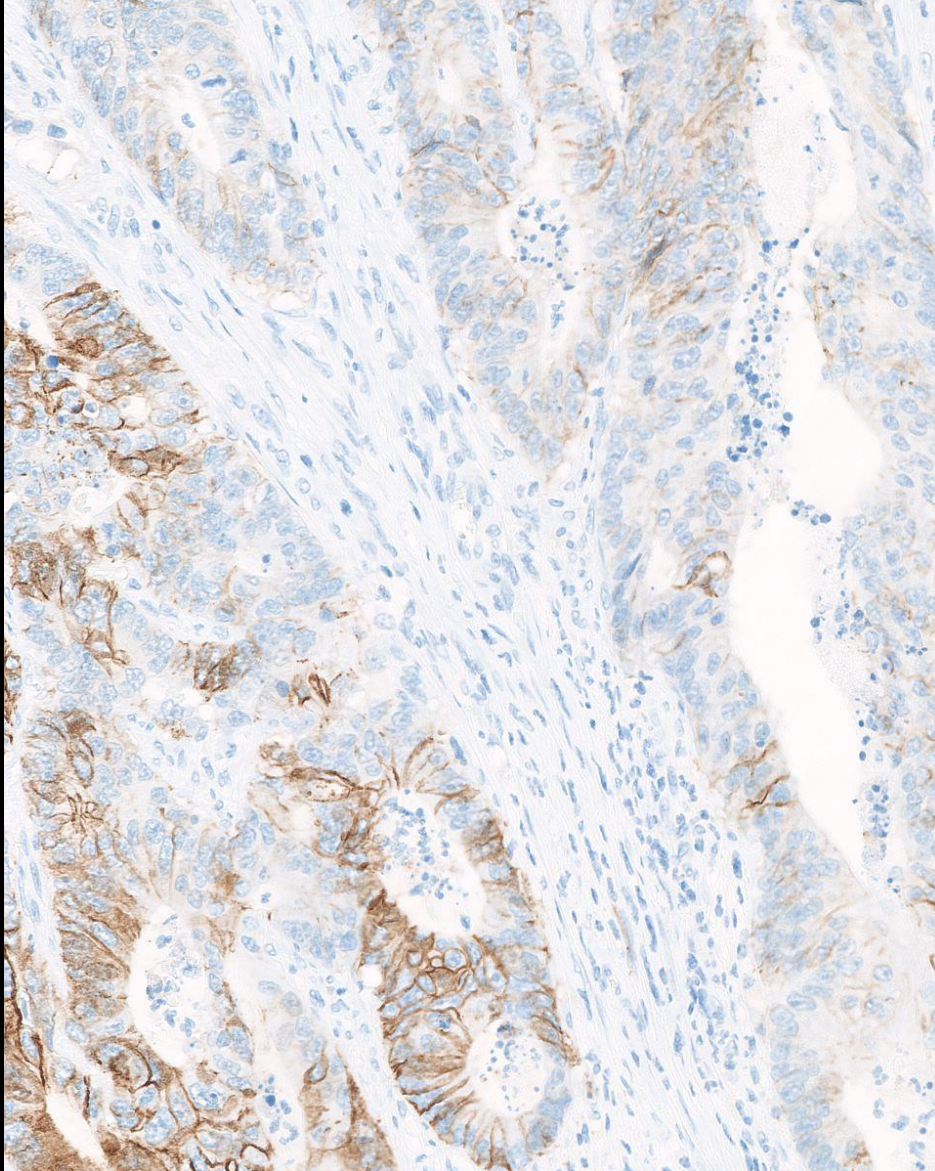


Cadherin 17: rmAb SP183, CM, 1:50,
CC1M/16M/UV

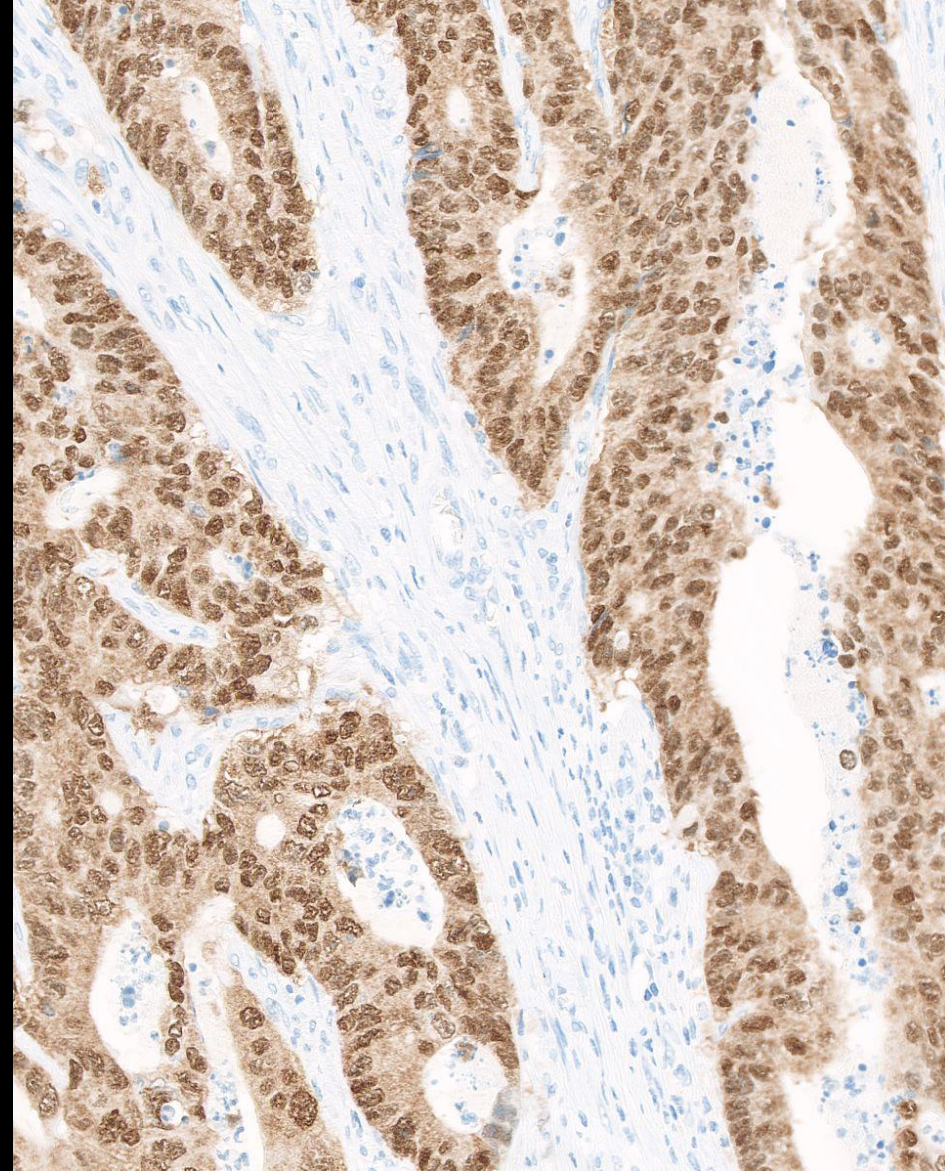


CDX2:
rmAb EPR2764Y, CM

CAD17 and CDX2 – Colon adenocarcinoma

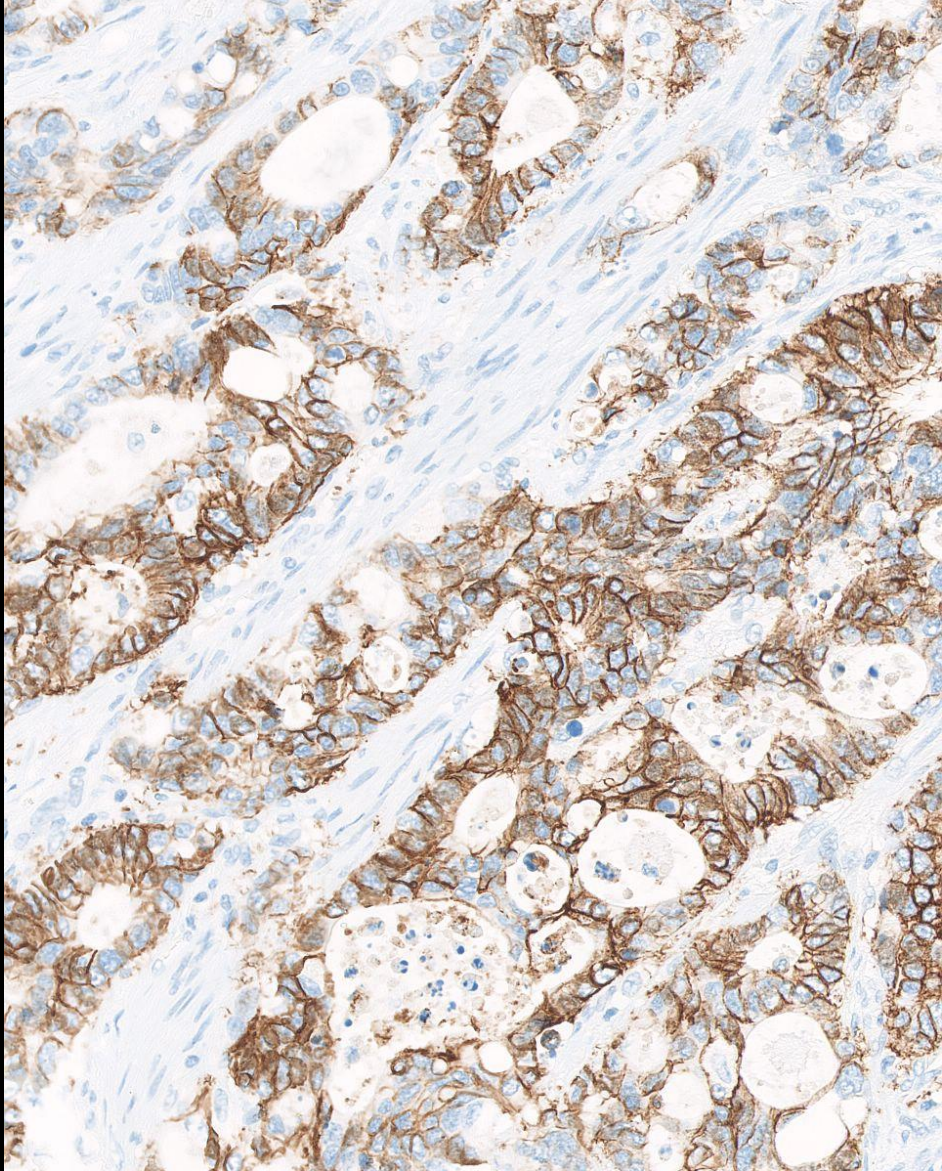


Cadherin 17: rmAb SP183, CM, 1:50,
CC1M/16M/UV

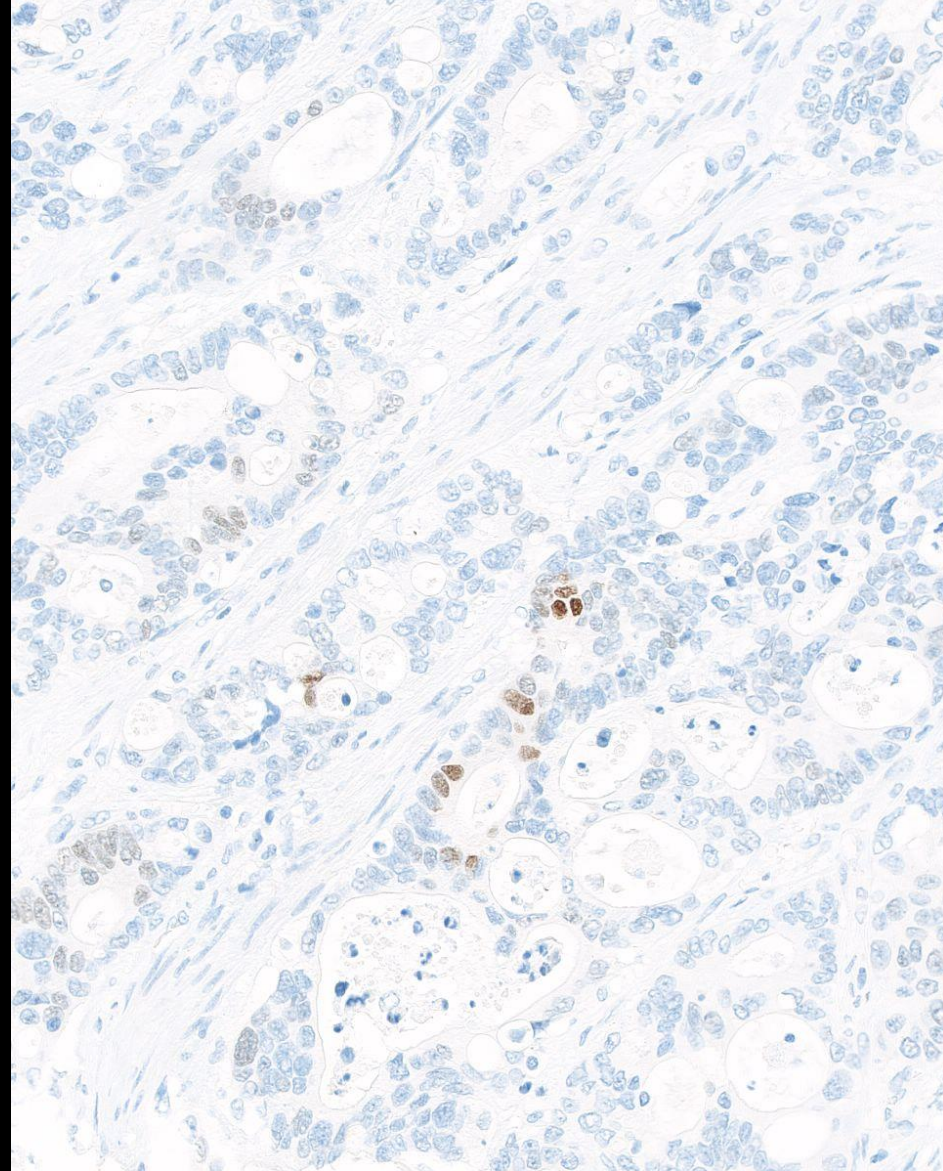


CDX2:
rmAb EPR2764Y, CM

CAD17 and CDX2 – Colon adenocarcinoma

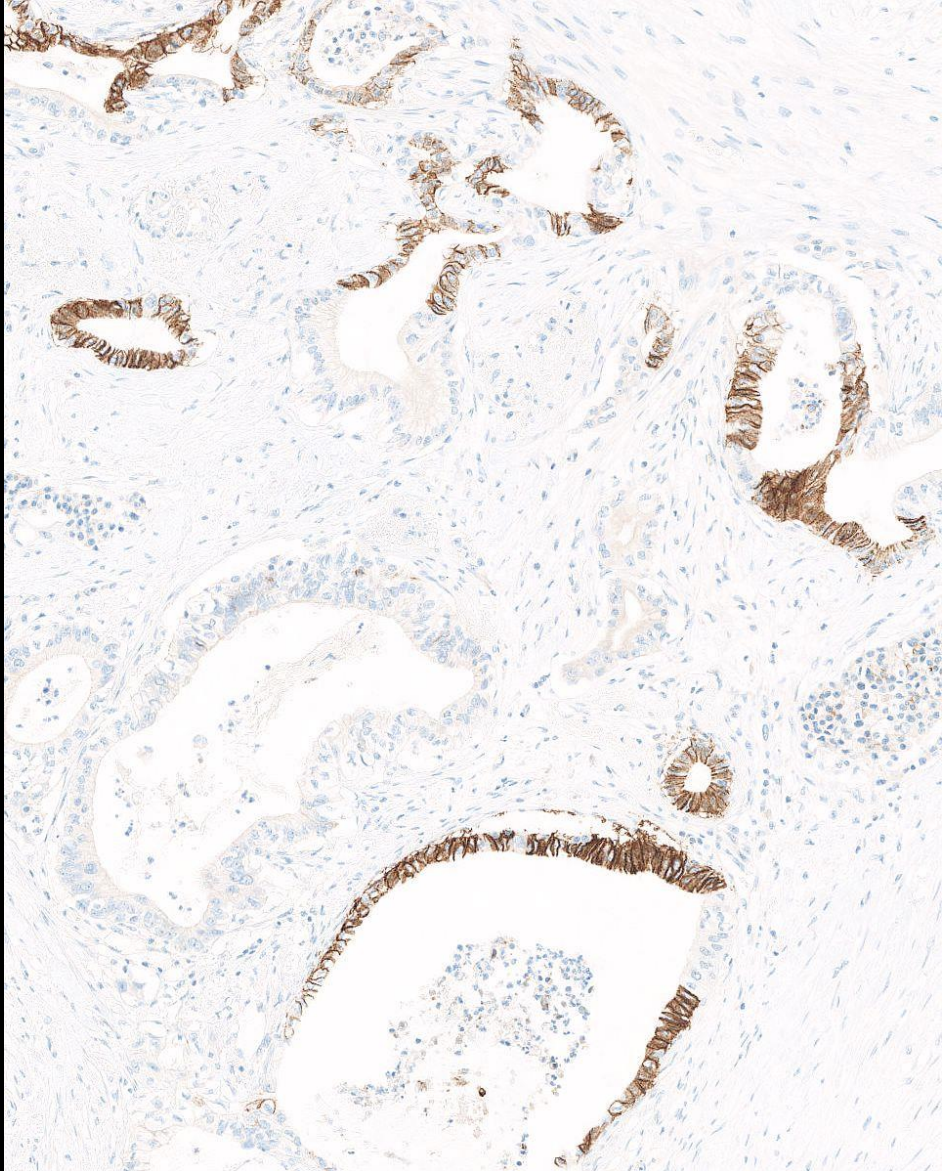


Cadherin 17: rmAb SP183, CM, 1:50,
CC1M/16M/UV

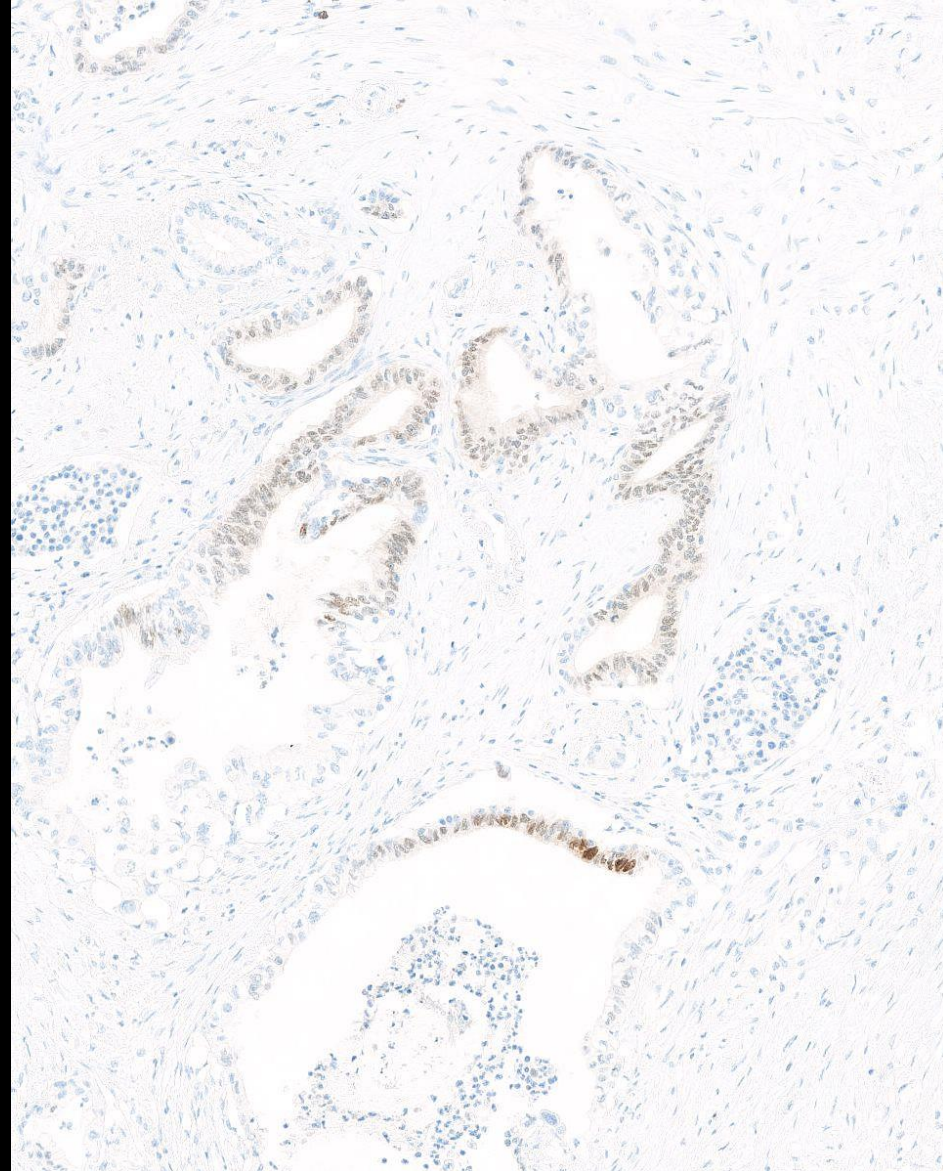


CDX2:
rmAb EPR2764Y, CM

CAD17 and CDX2 – Pancreas adenocarcinoma



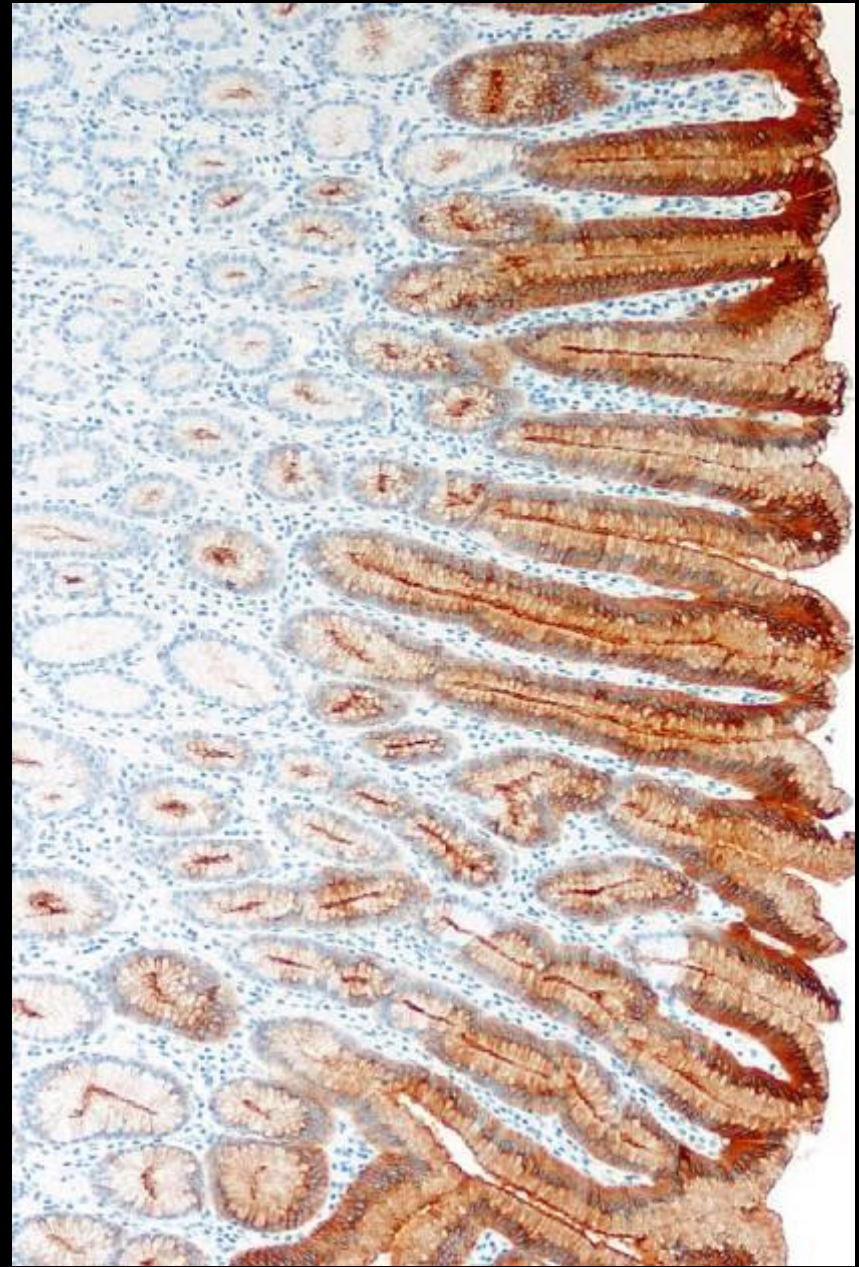
Cadherin 17: rmAb SP183, CM, 1:50,
CC1M/16M/UV



CDX2:
rmAb EPR2764Y, CM

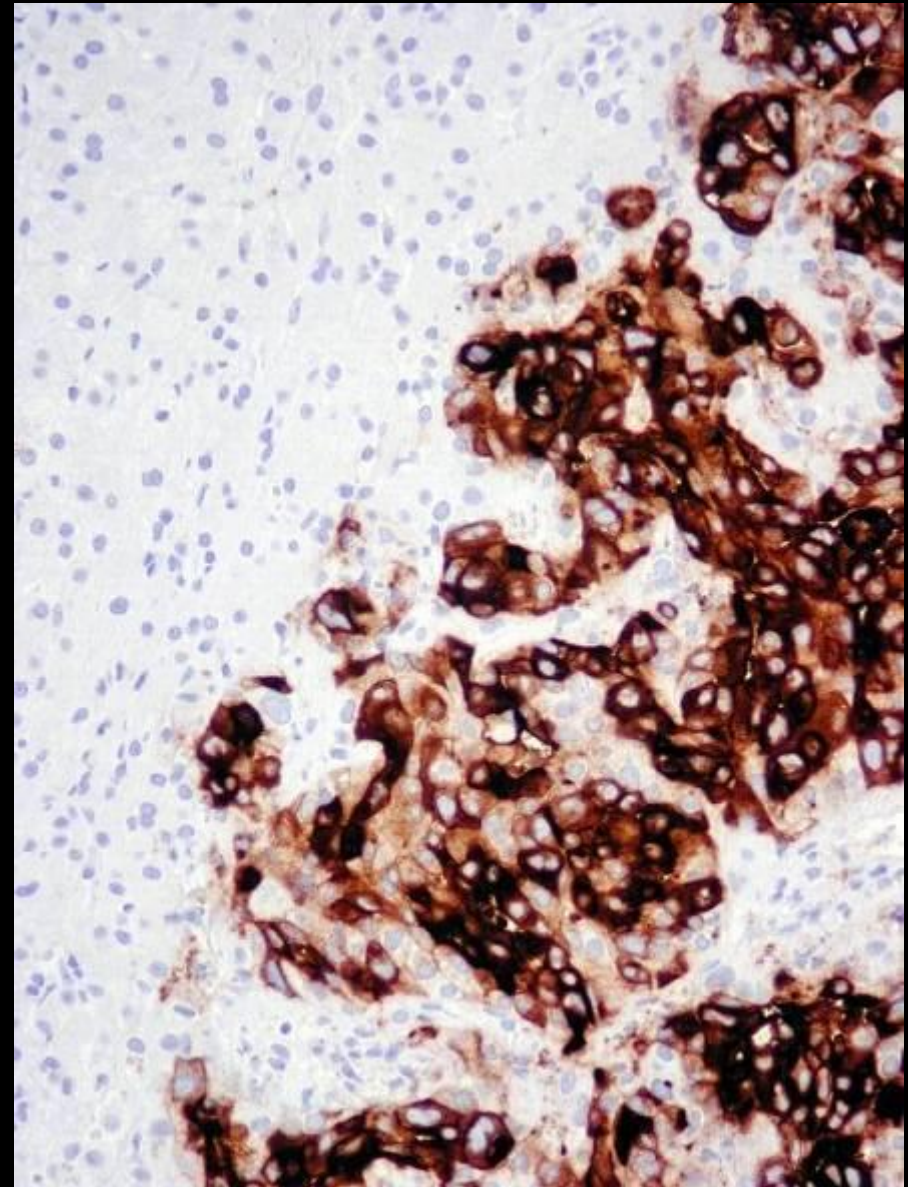
Carcinoembryonic antigen (CD66e)

- Adhesion molecule espc. associated with intestine



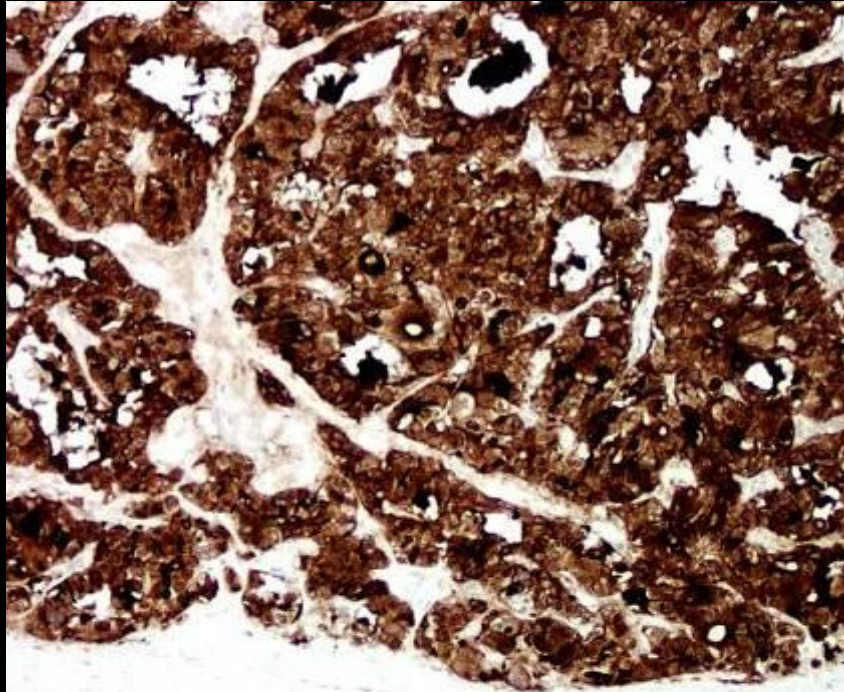
Carcinoembryonic antigen (CD66e) in adenocarcinomas

- Colorectal +
- Medull. thyroid +
- Pancreas/biliary tract +/-
- Stomach +/-
- Lung +/-
- Ovary, mucinous +/-
- Ovary, non-muc. -/+
- Prostate -
- Kidney -
- Liver (!) -

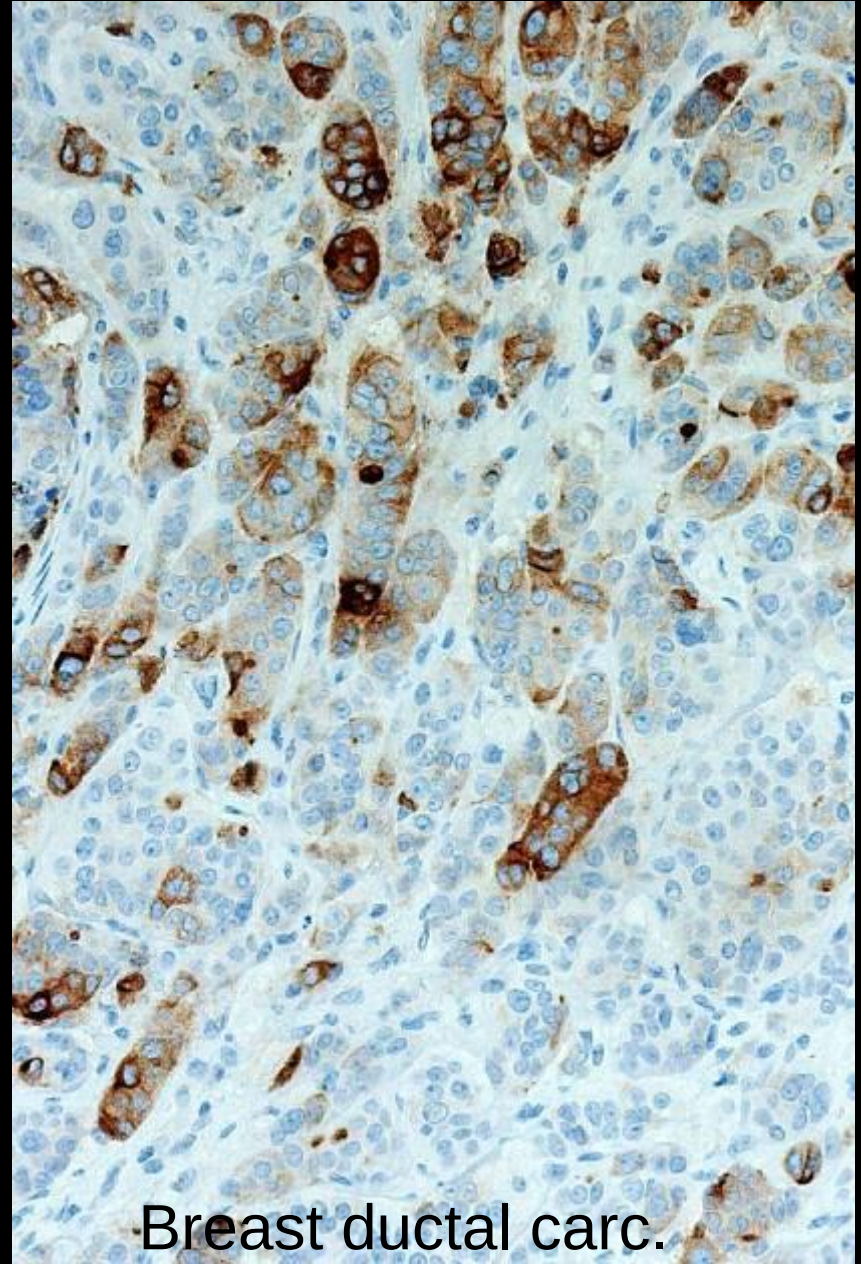


metast. colon adenoc

Carcinoembryonic antigen



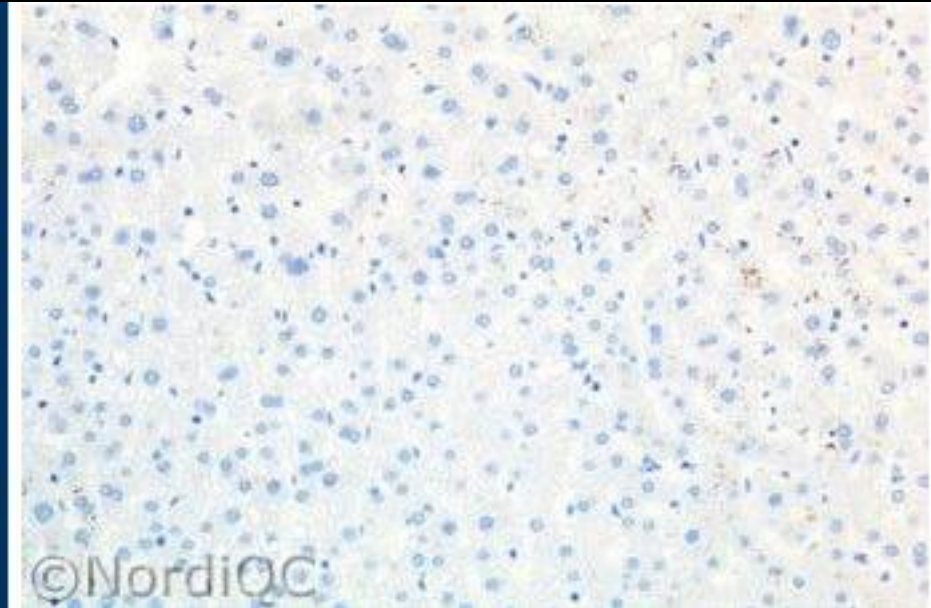
Medul. thyroid carc.



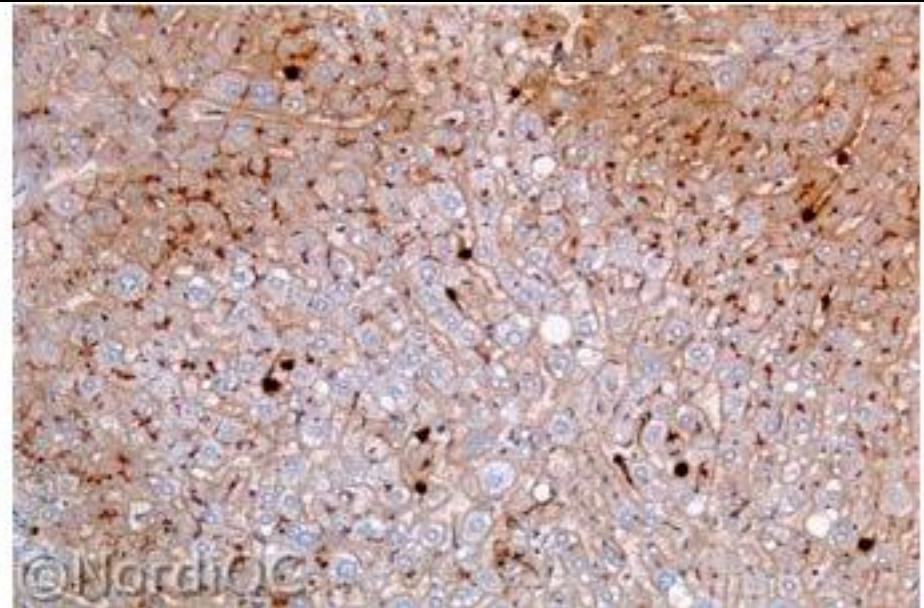
Breast ductal carc.

Carcinoembryonic antigen – which antibody?

Normal liver

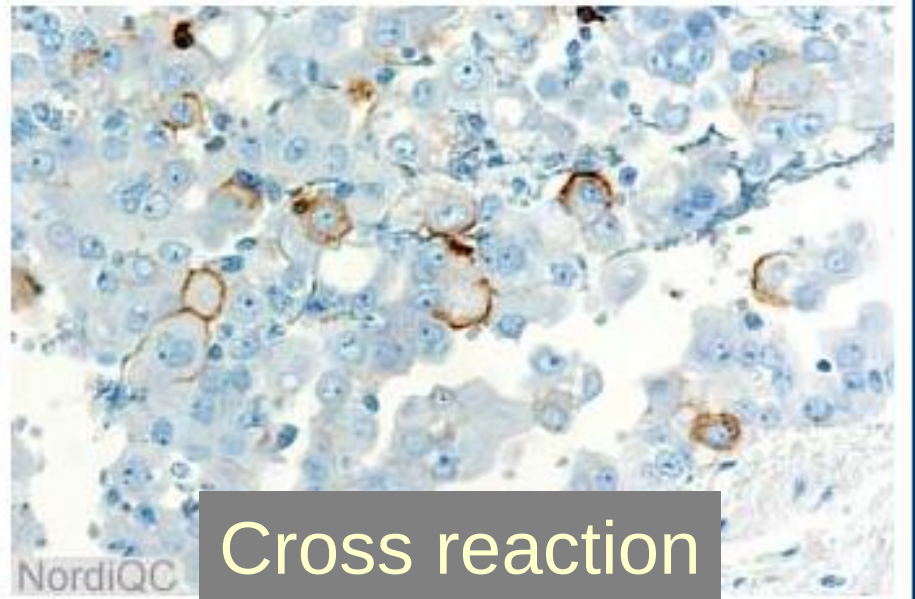


II-7

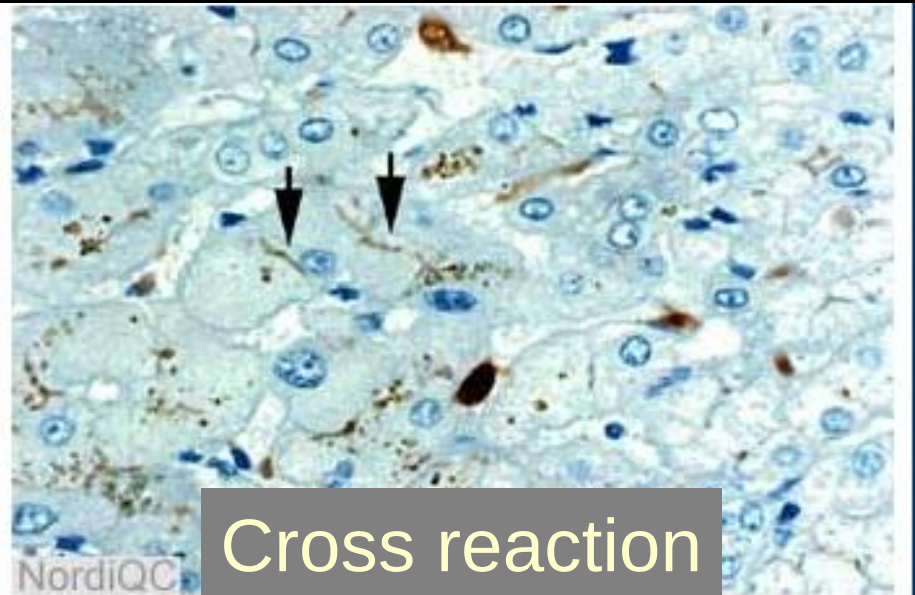


TF3H8-1

Malignant mesothelioma



Normal liver



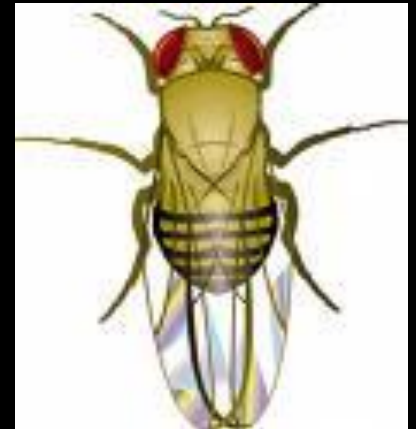
SMAD4

Similar to Mothers Against Drosophila 4 =

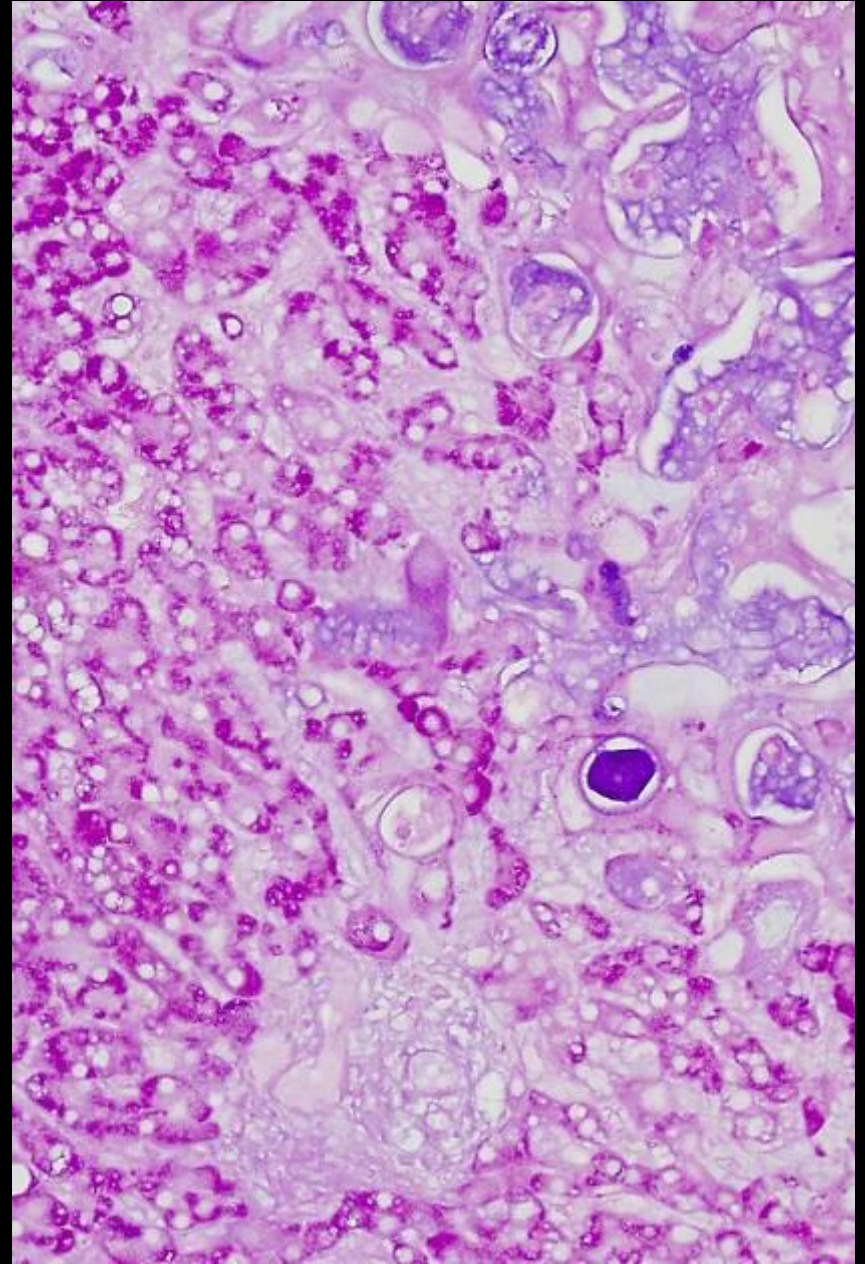
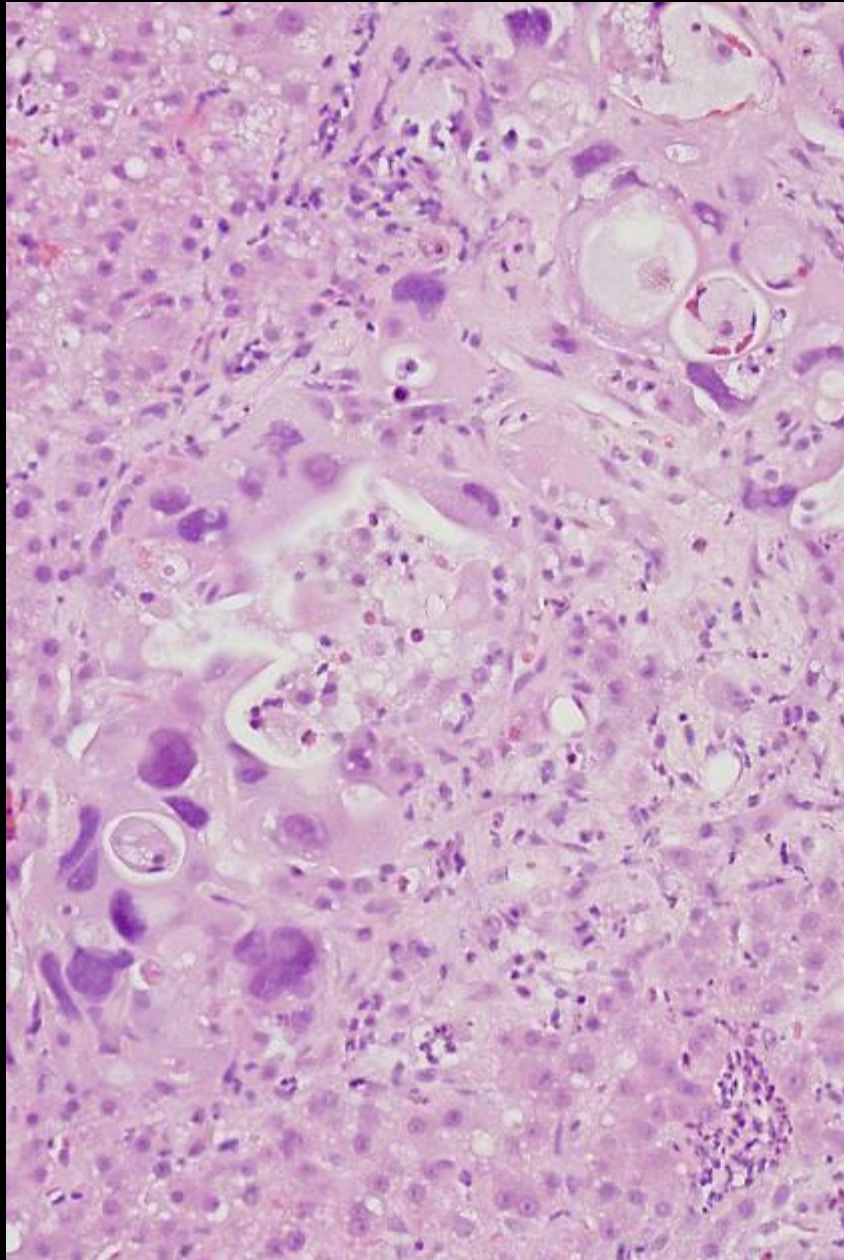
Deleted in pancreatic cancer-4 (DPC4)

Nuclear transcription activator in all normal cells

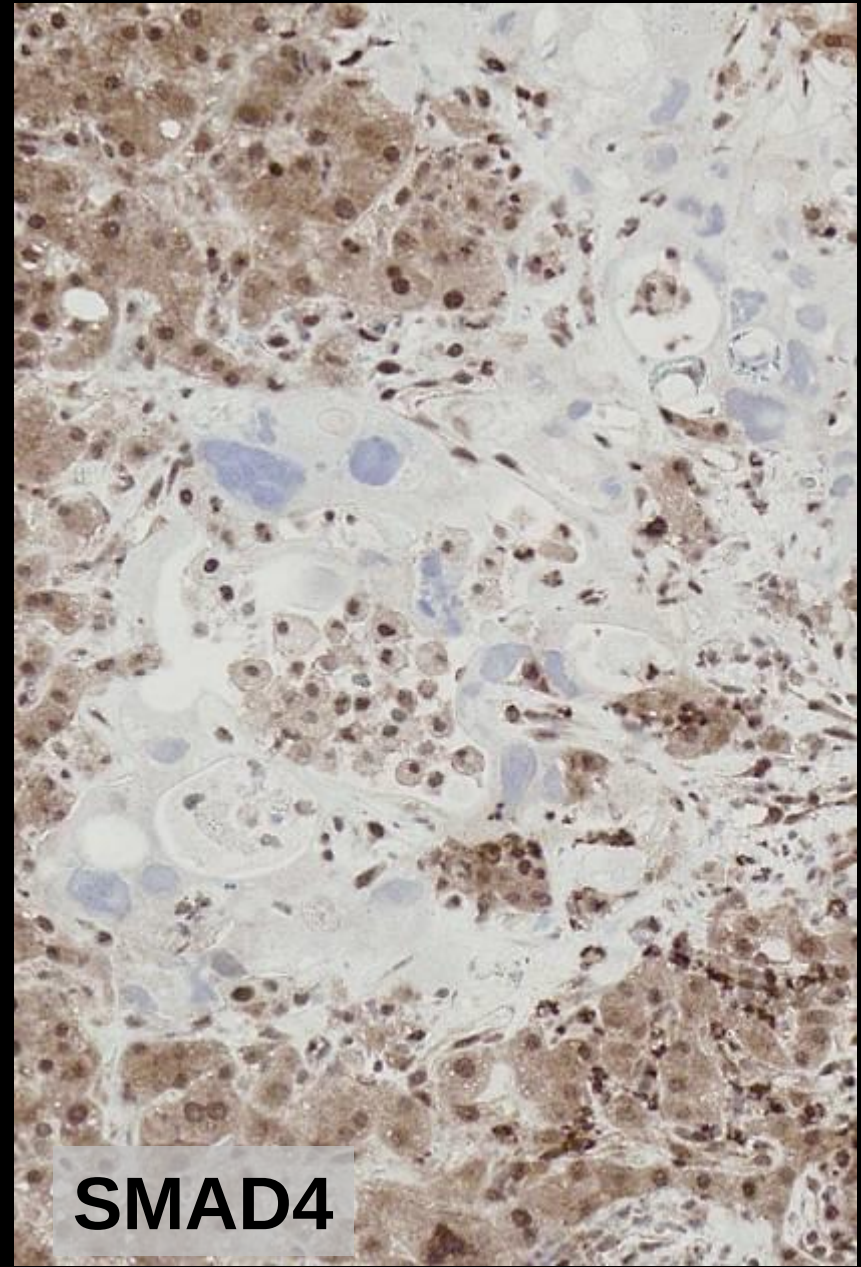
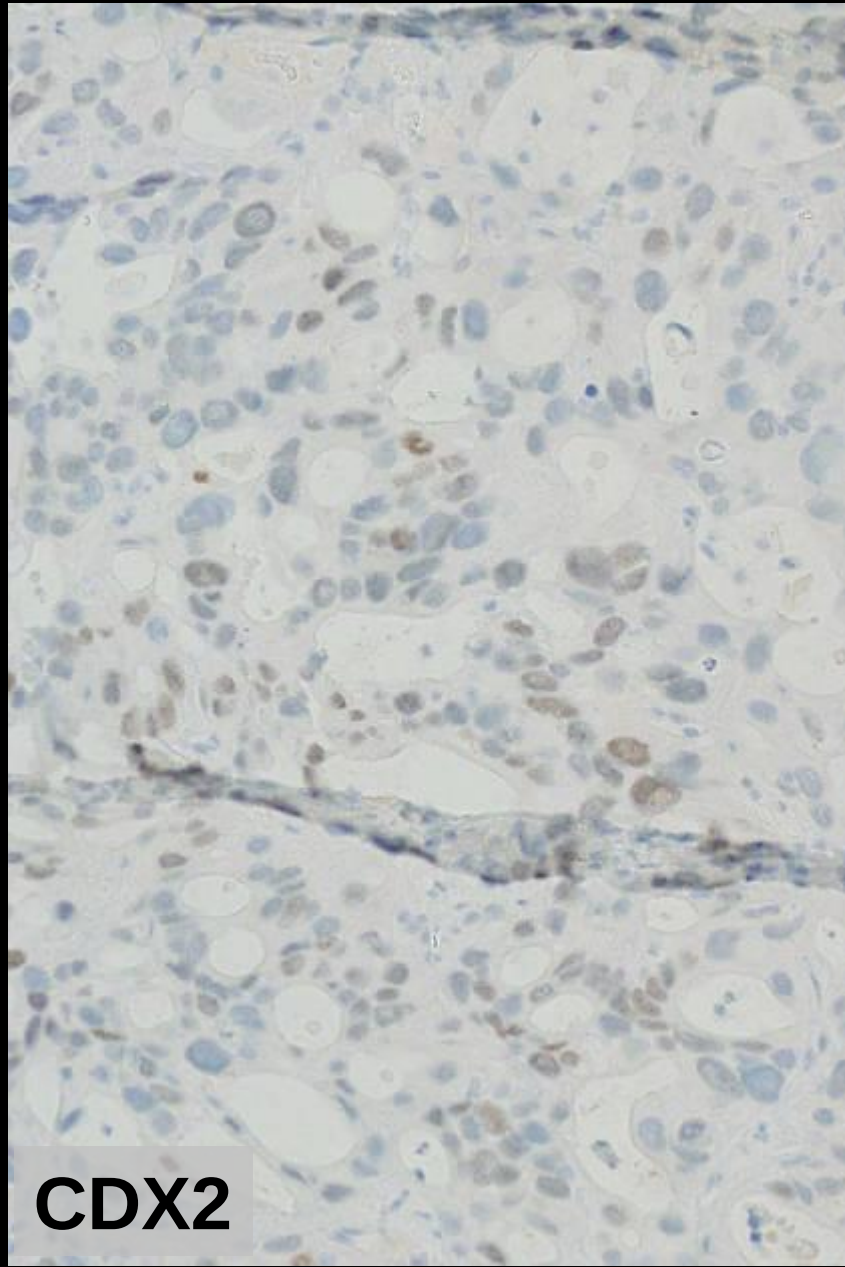
- Deleted in ~ 50% of pancreatic carcinomas
- Deleted much less frequently in other carcinomas
- Marker of invasive growth (?)



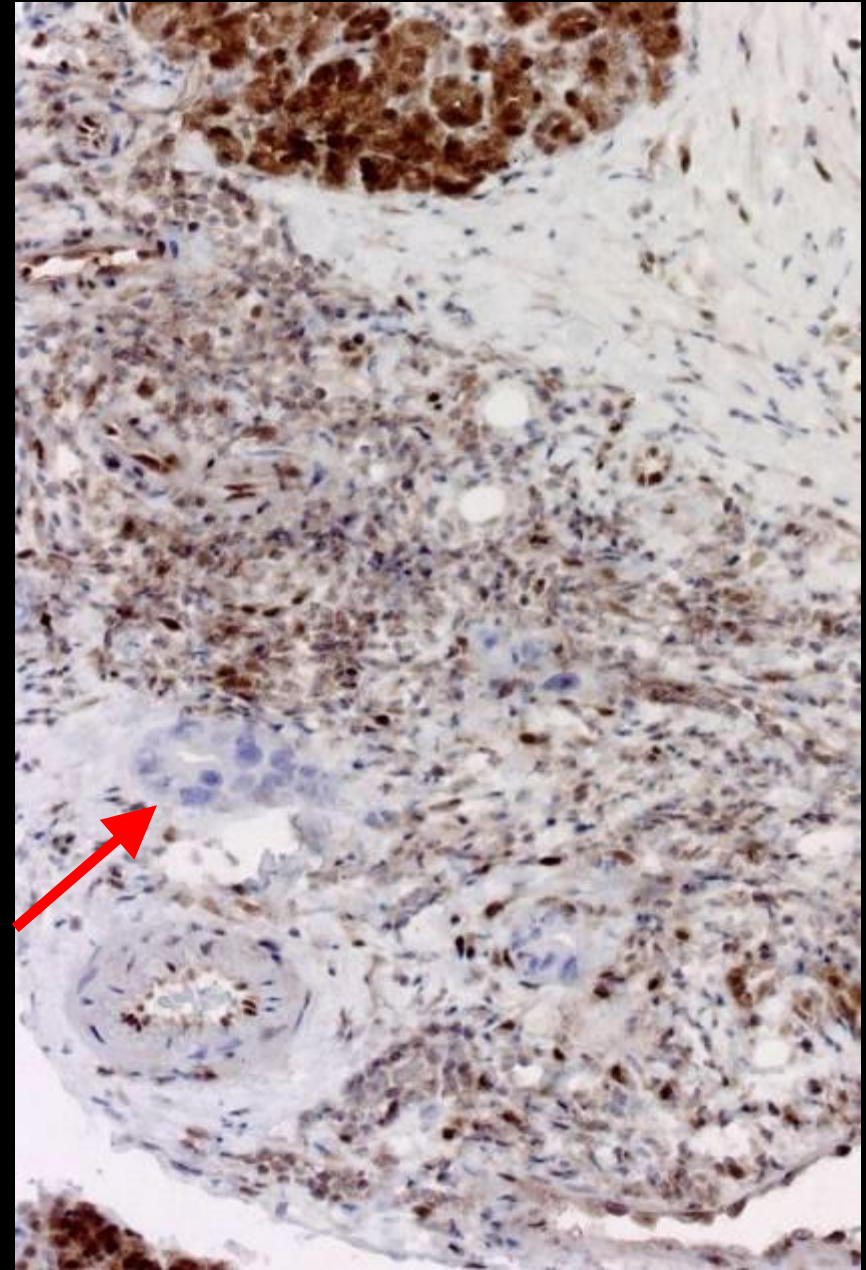
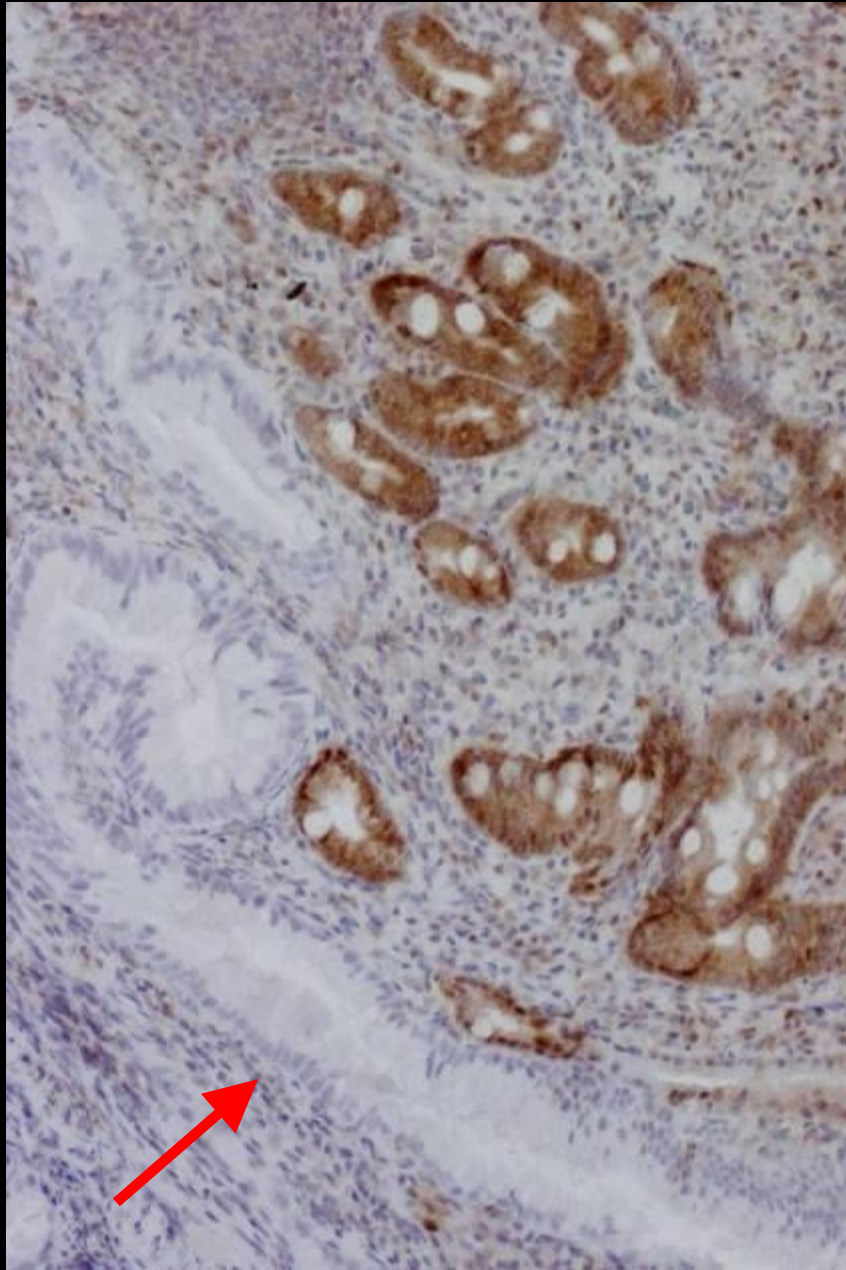
♂ 53 – liver with ACUP



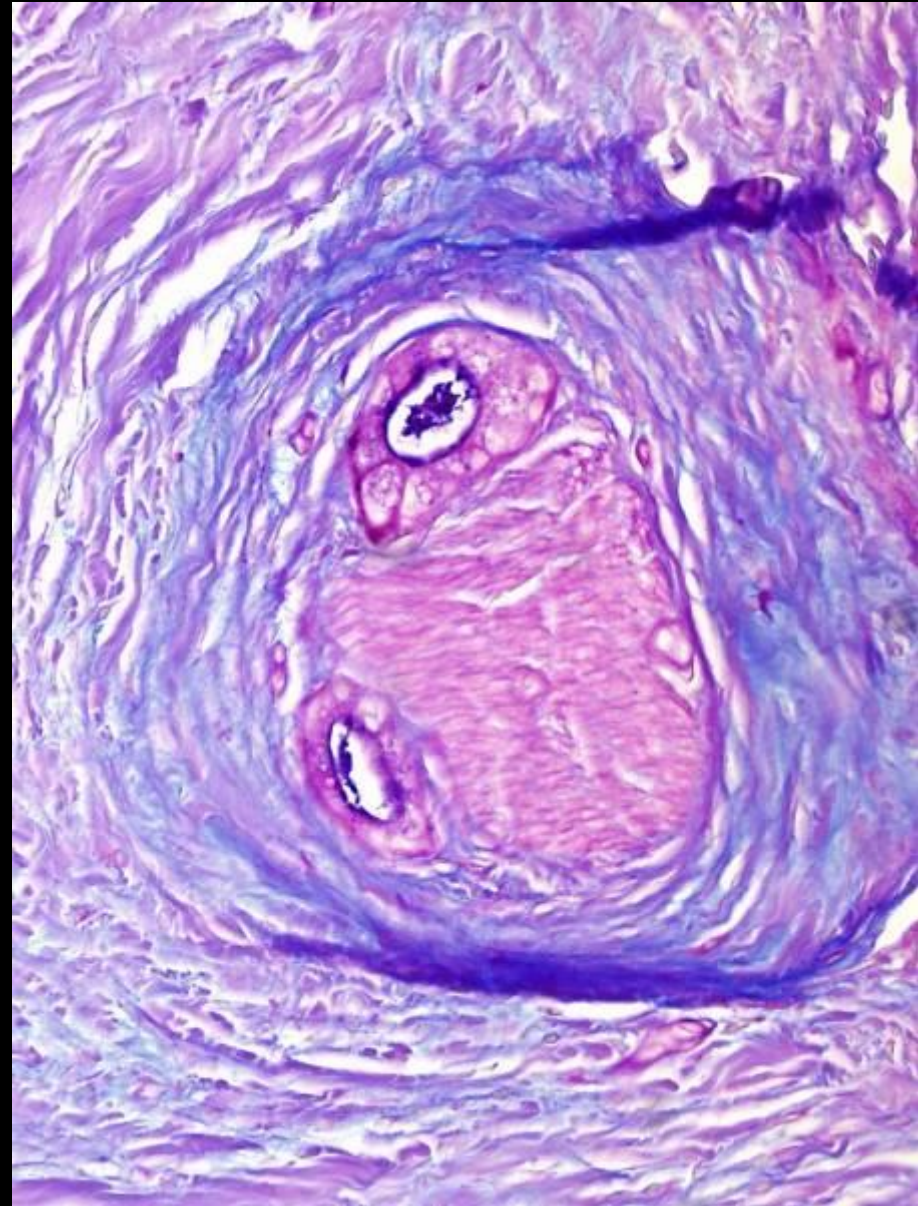
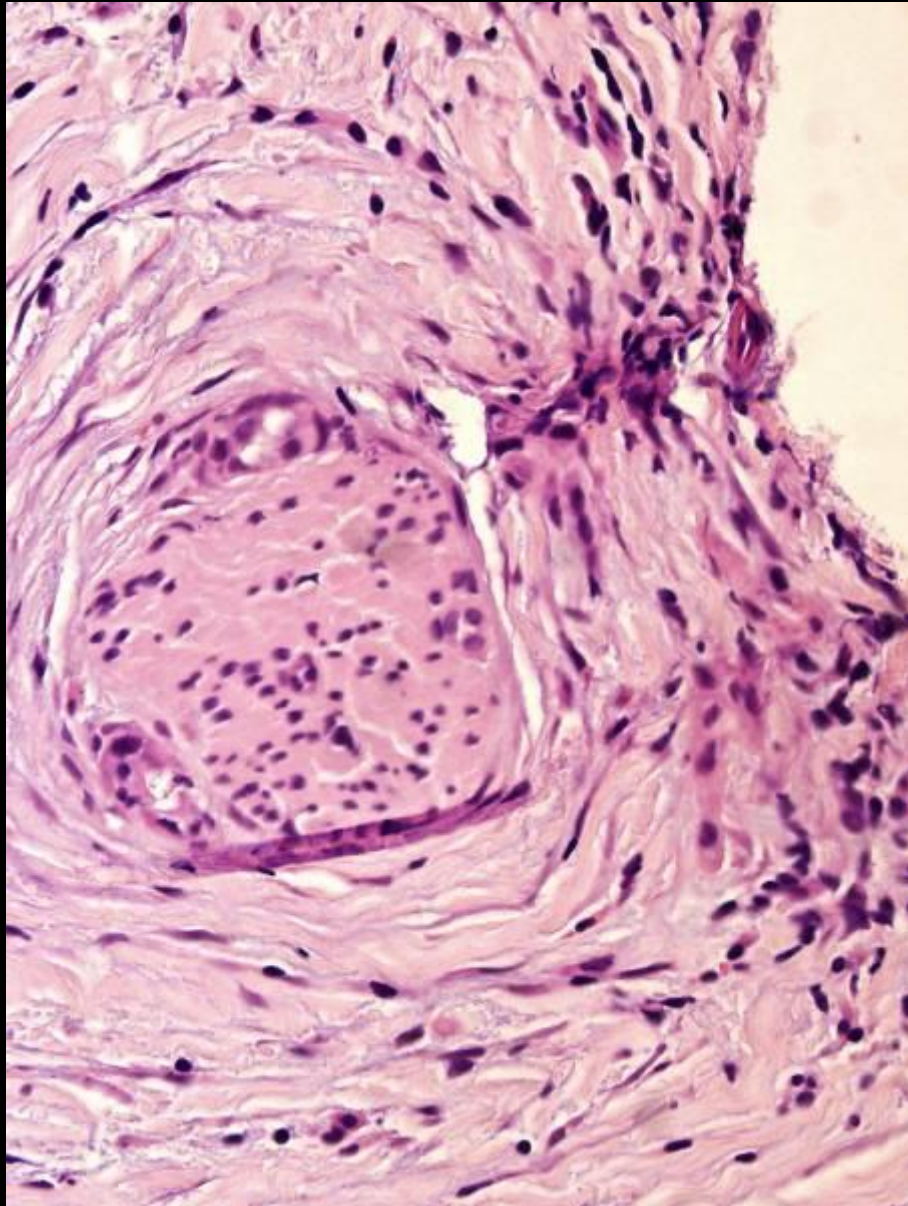
♂ 53 – liver with ACUP



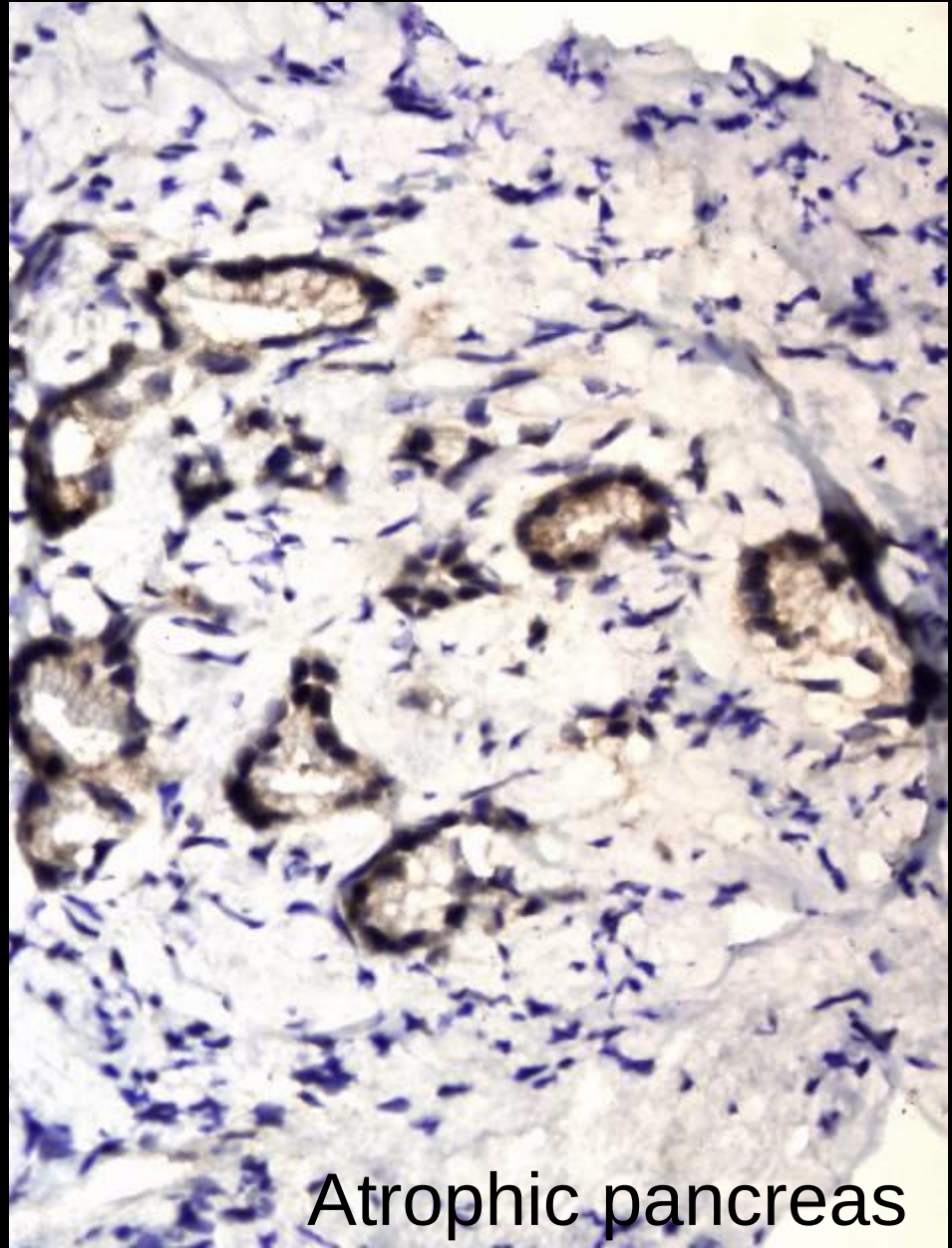
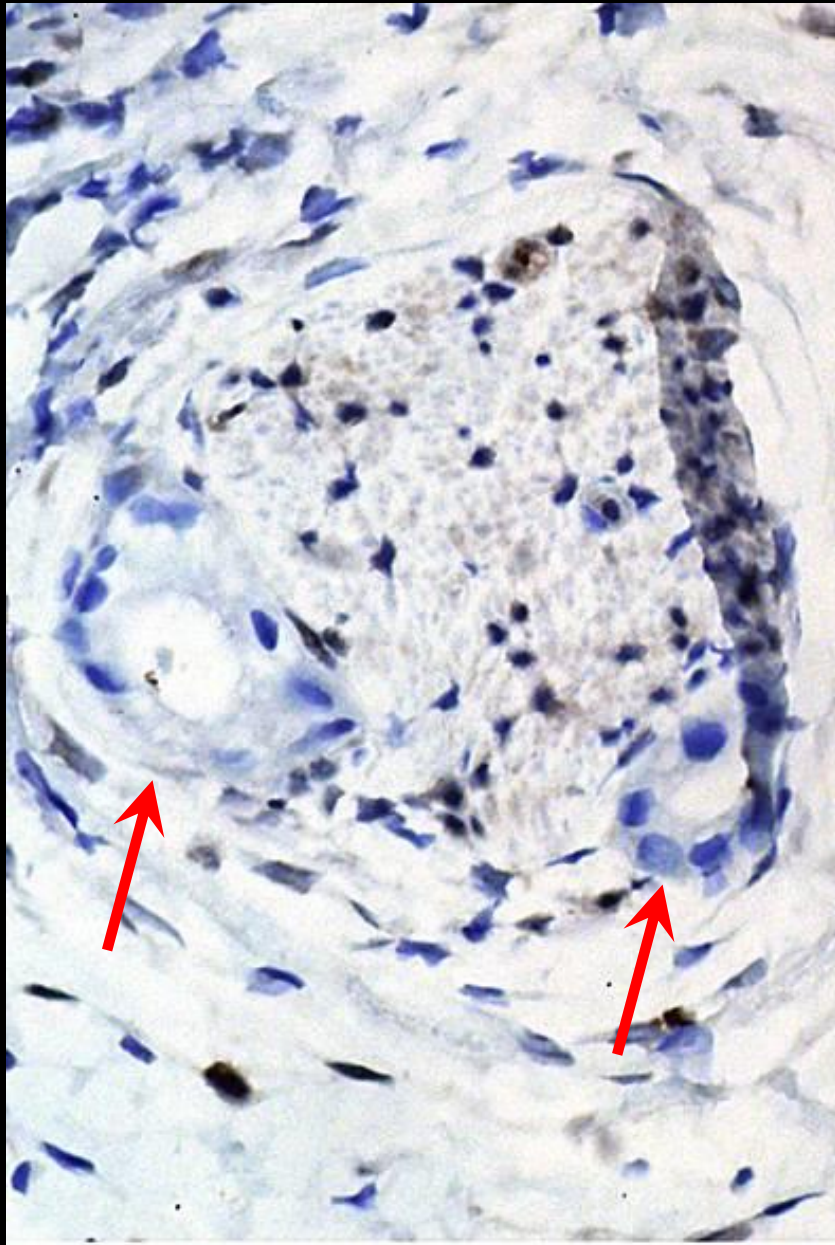
SMAD4 loss in pancreatic and ampullary carcinomas



“Glands” in pancreatic nerve



SMAD4 loss in “glands” in pancreatic nerve



Atrophic pancreas

“Female genital tract markers”

CA125

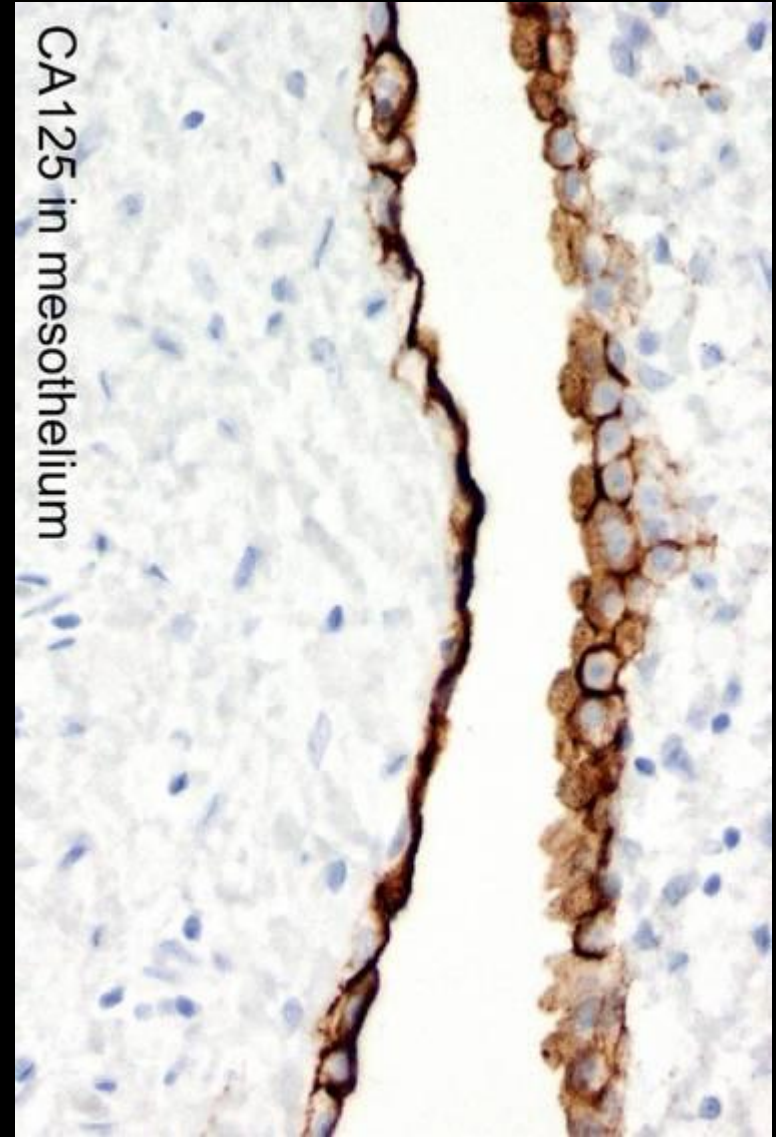
PAX8

WT1

Cancer antigen 125

Oncofetal glycoprotein. In fetal life associated with amnion, coelomic and Müllerian epithelium

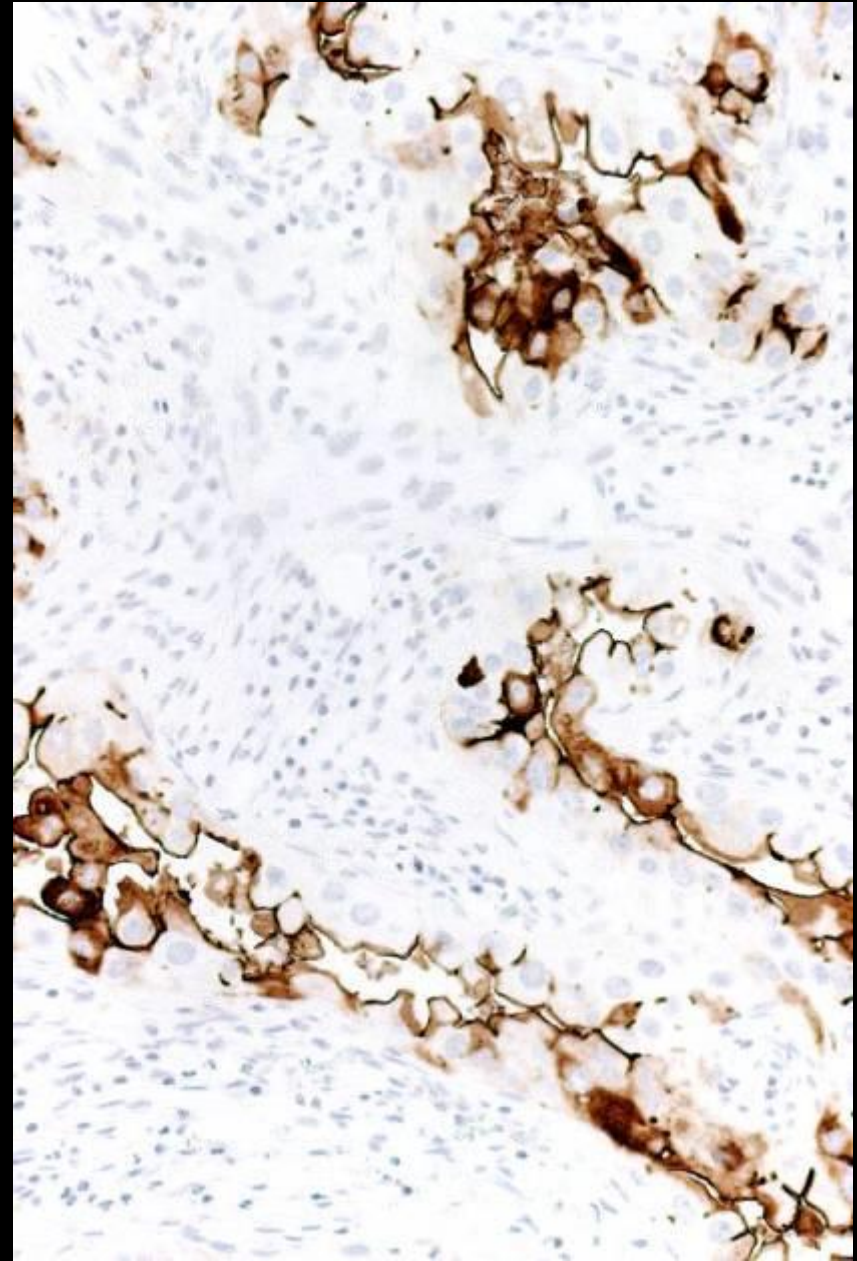
- Mesothelial cells (visceral)
- Epithelial cells of
 - Female genital tract
 - Breast
 - Pancreas / biliary tract
 - Apocrine sweat glands



Cancer antigen 125 in carcinomas and look-alikes

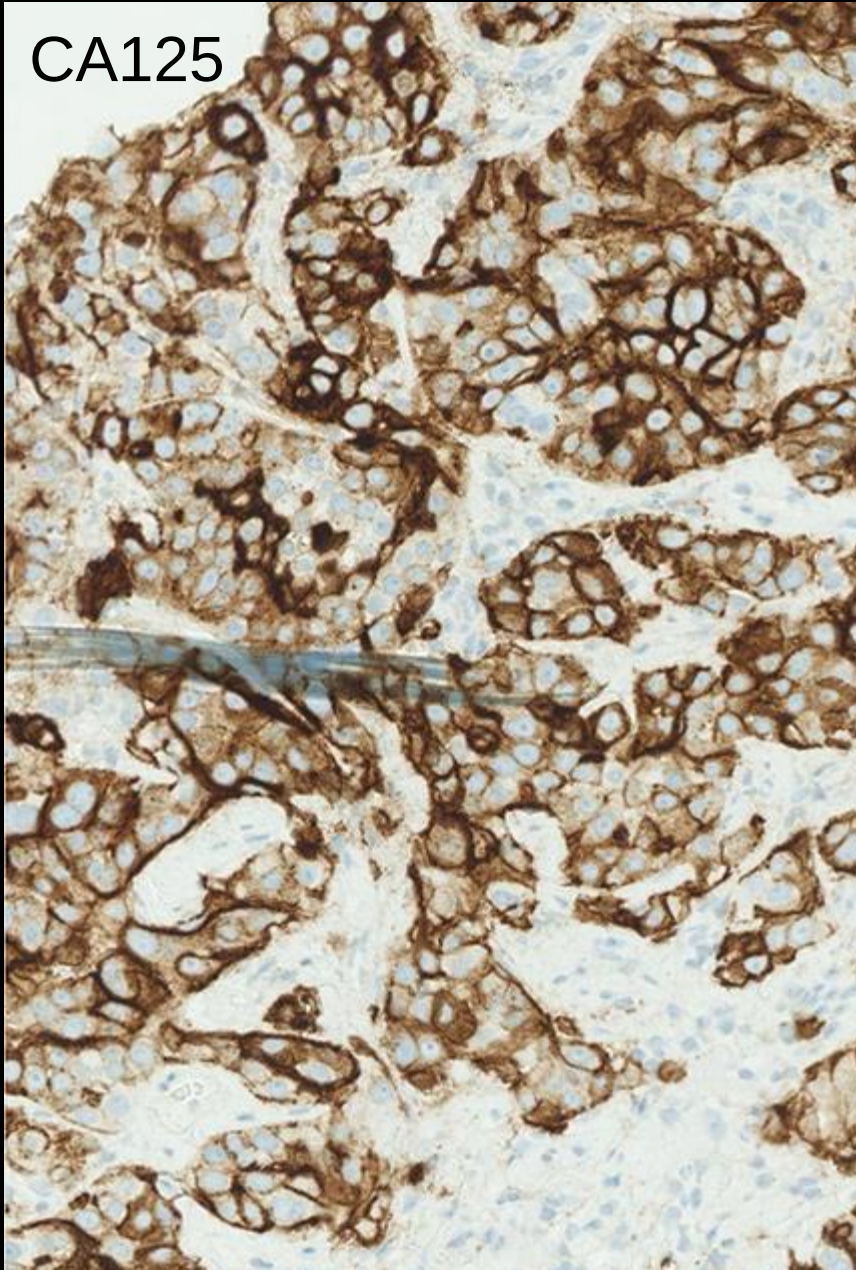
■ Mal. mesothelioma	+/-
■ Serous ovarian	+
■ Endometrioid	+/-
■ Cervical	+/-
■ Pancreas/bil.	+/-
■ Lung	-/+
■ Breast	-/+
■ Colorectal	-/+
■ Renal carcinoma	-(+)
■ Prostate	-(+)

Pancreas adenocarc.

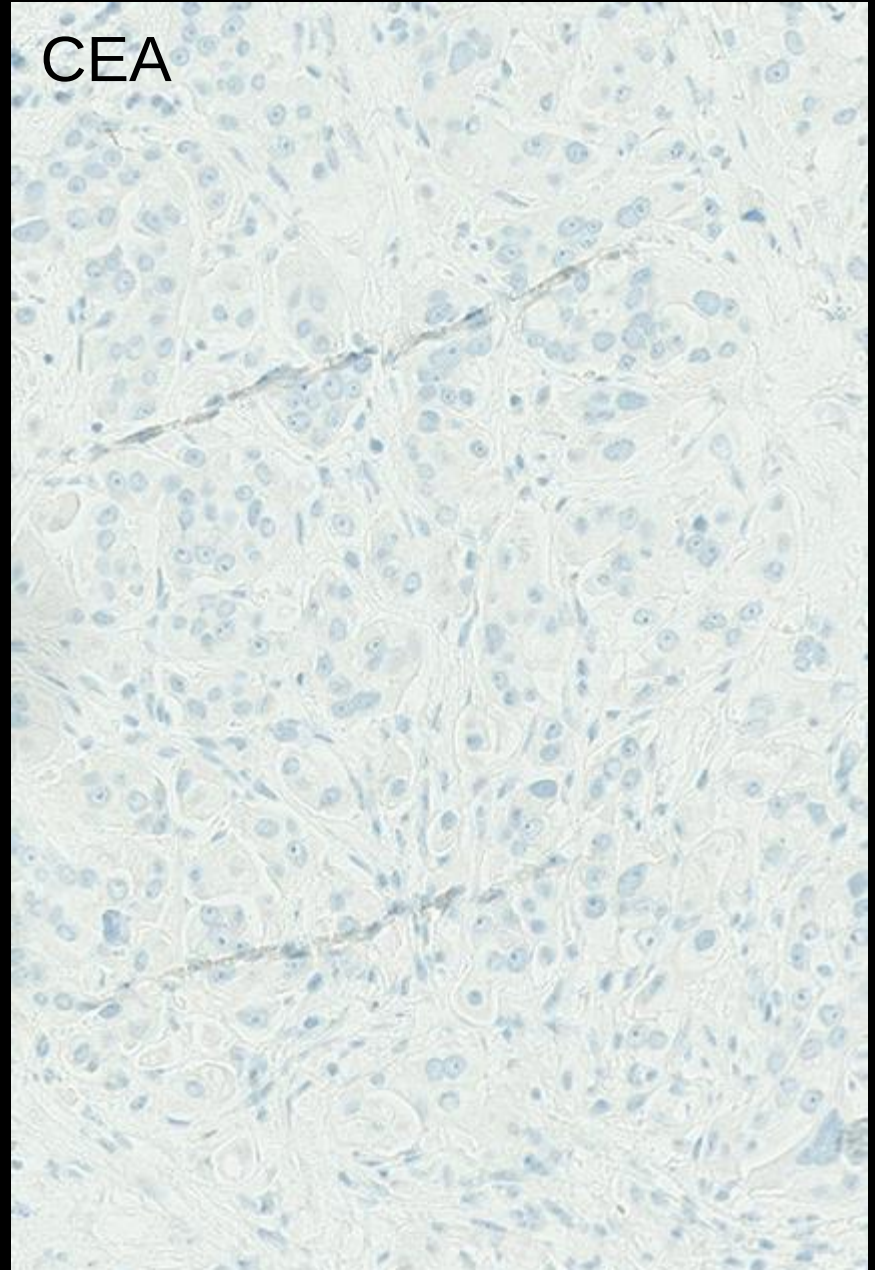


Ovarian serous carcinoma

CA125

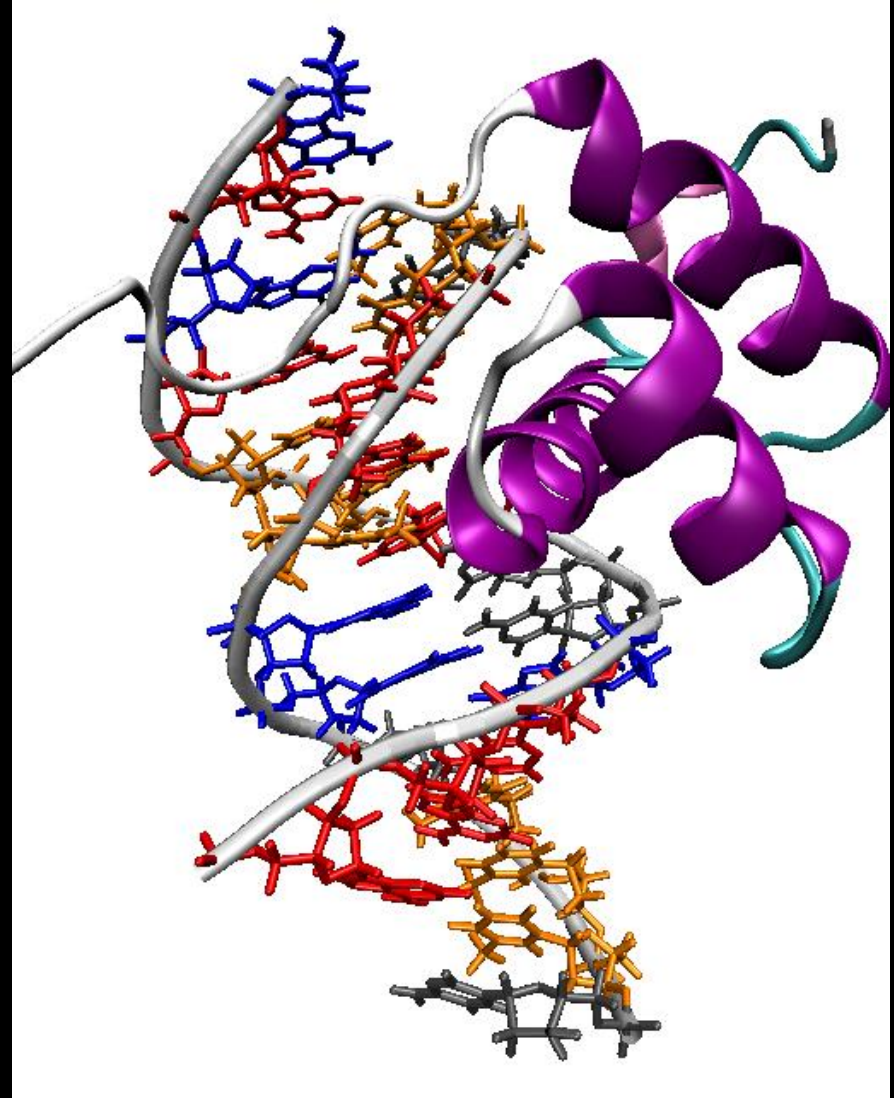


CEA



Paired box (PAX) gene proteins

- Family of tissue specific transcription factors containing a paired domain and usually a partial or complete homeodomain.
- Important in early development for the specification of tissues, regulating cell proliferation, migration, and resistance to apoptosis



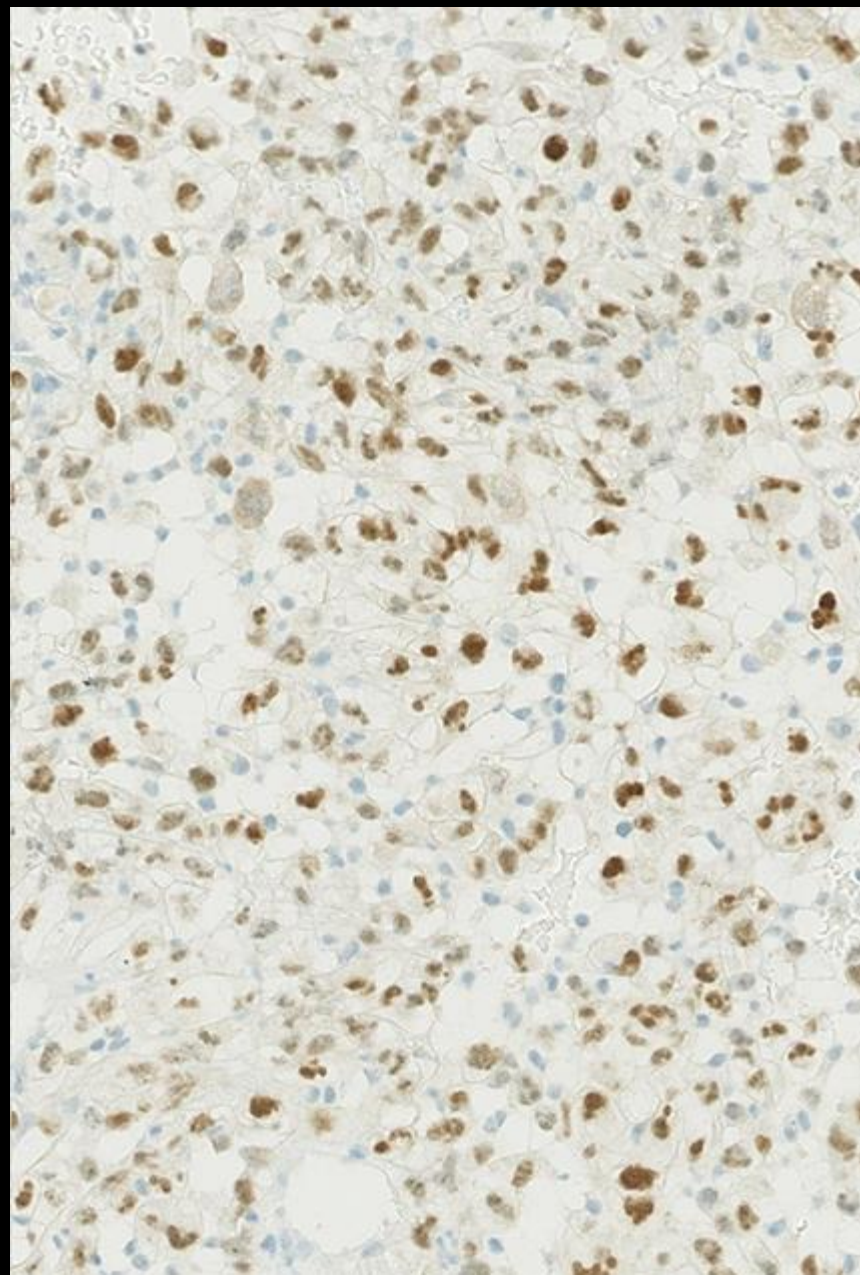
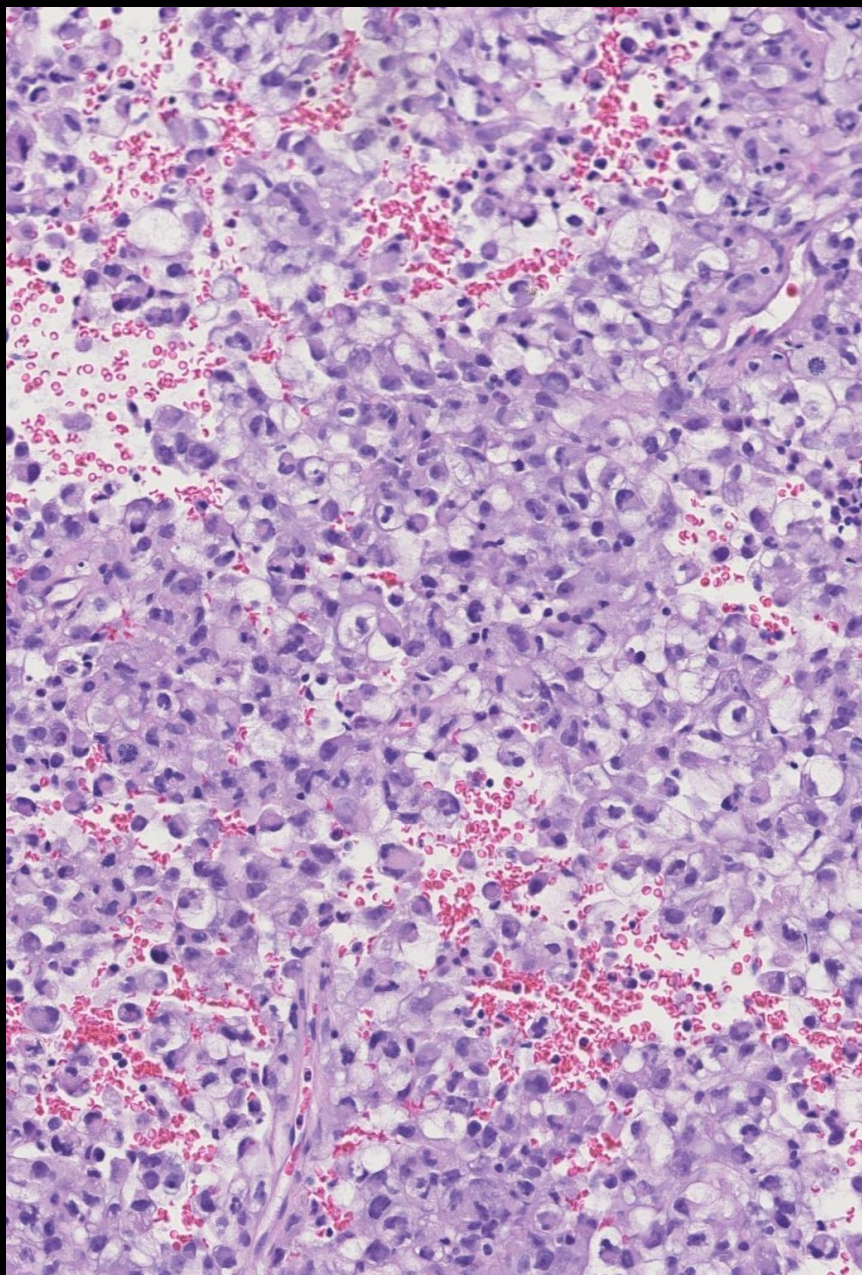
Crucial to the organogenesis and development of

- Urogenital tract
- Adult genital tract
- Thyroid
- Neuroendocrine system

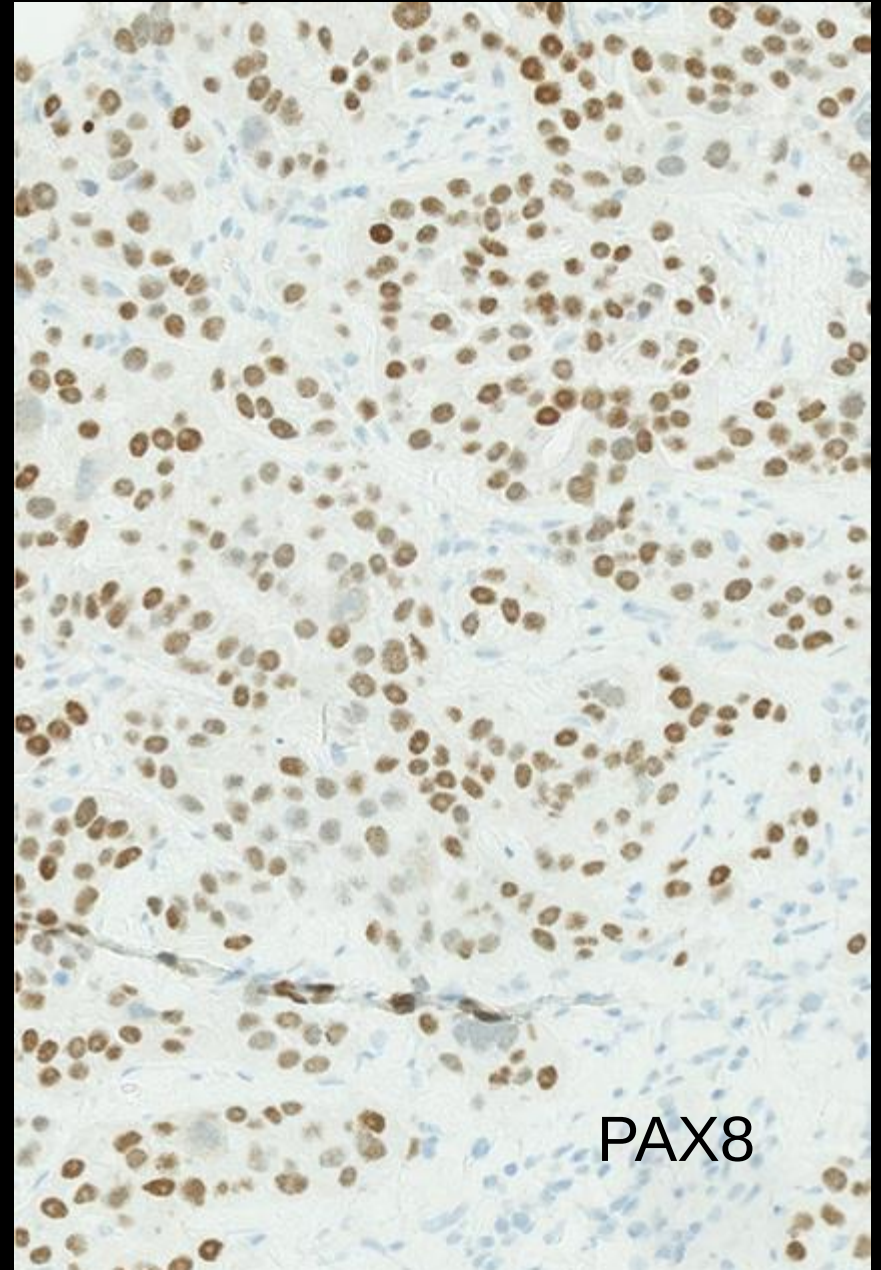
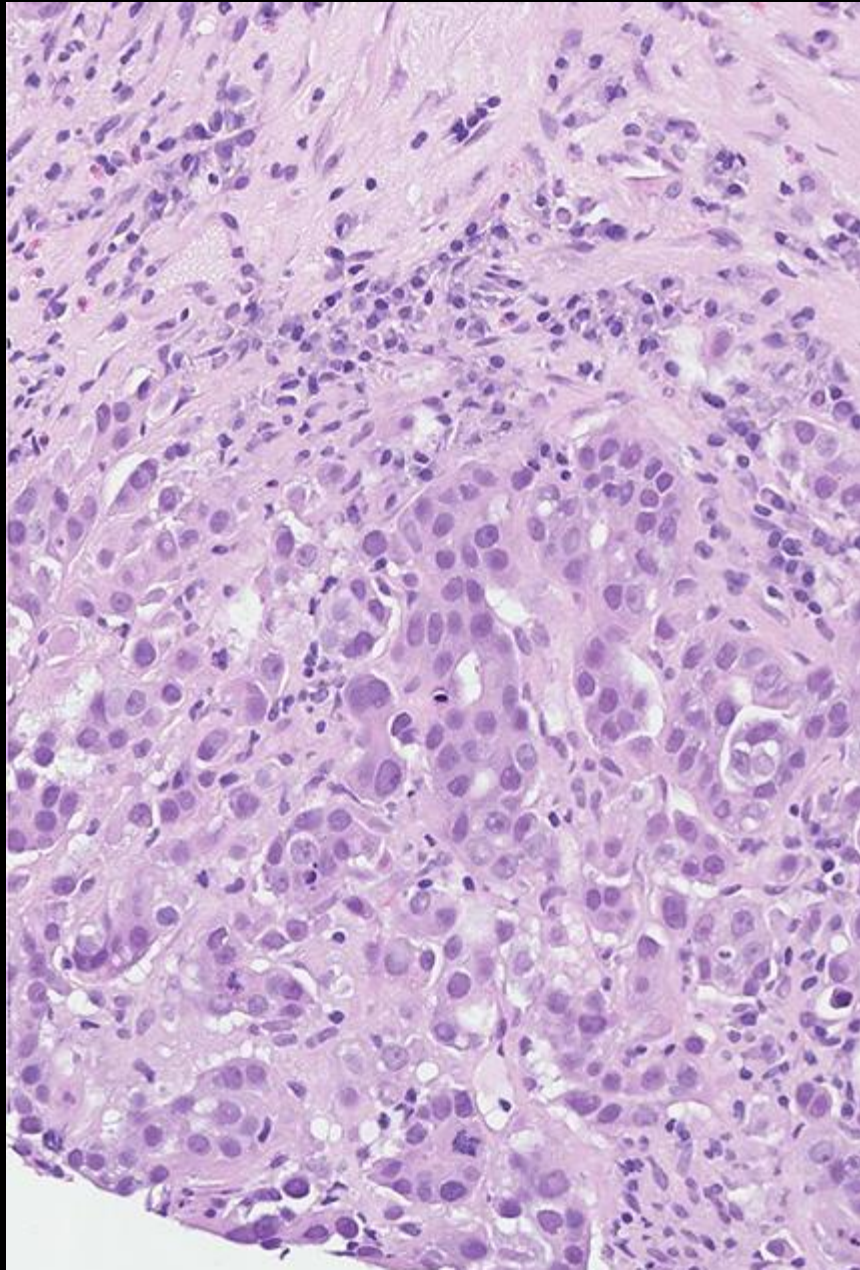
PAX8

Ovary - serous carcinoma LG	+
- serous carcinoma HG / clear cell	+
- endometrioid carcinoma	+/-
- mucinous carcinoma	-(+)
Kidney - clear cell / papillary carcinoma	+
- chromophobe / collect. duct carc.	+
- RCC, sarcomatoid	+/-
NET - pancreas, duodenum, rectum	-(+)?
Thyroid carcinoma	+
Other carcinomas	-(+)
Malignant mesothelioma	-

PAX8 in clear cell renal cell carcinoma



Ovarian serous carcinoma



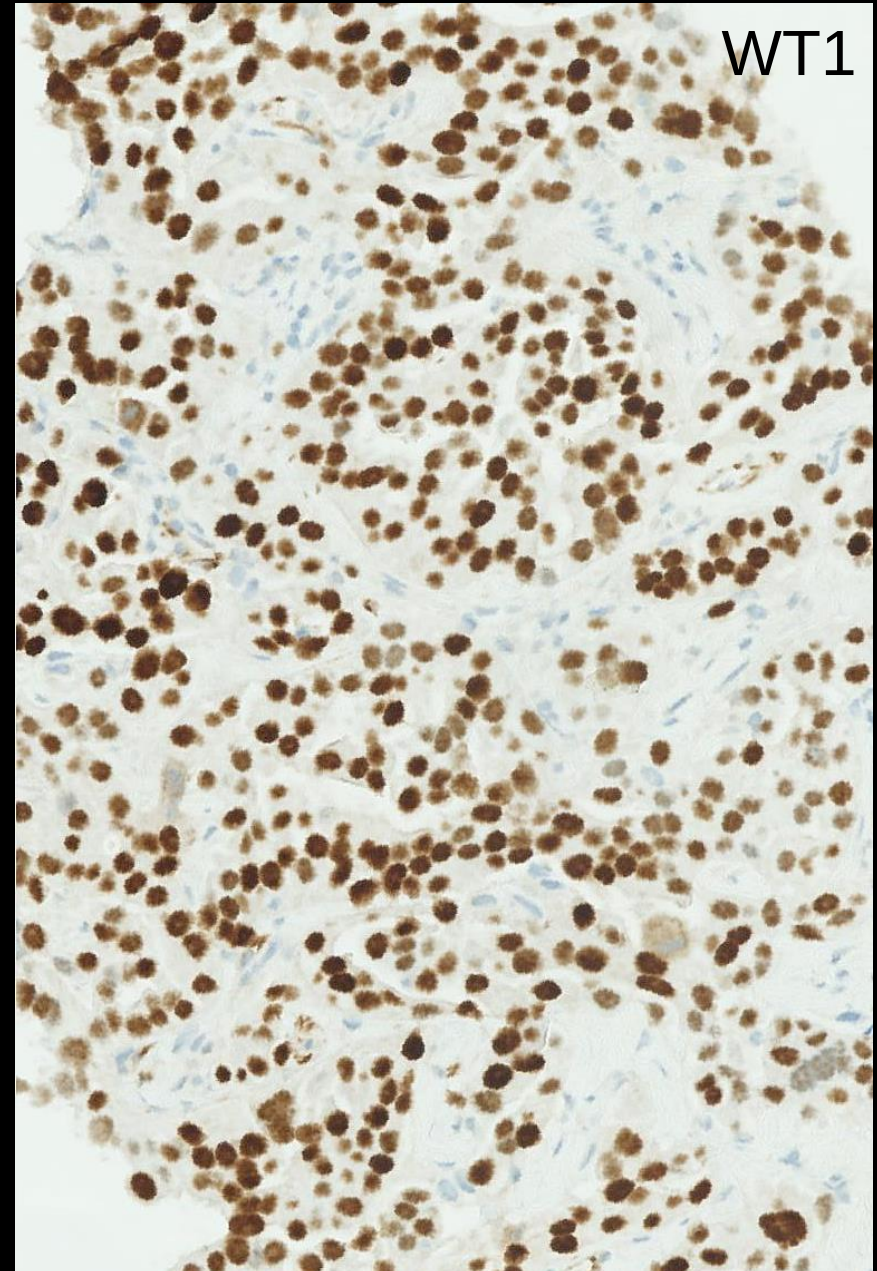
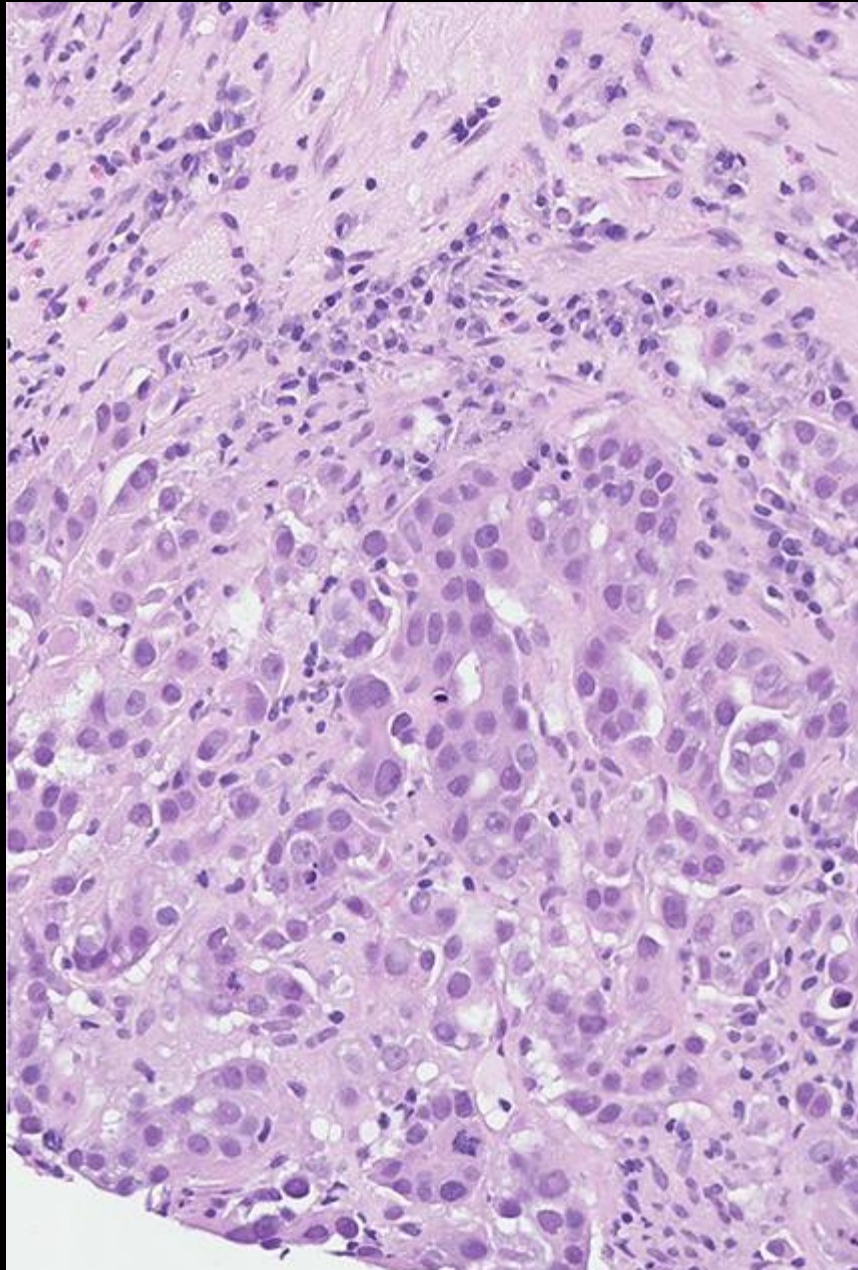
Wilms' tumour-1 (WT1) protein in carcinomas/mesotheliomas

- Serous carcinoma +
- Endometrioid carcinoma +/-
- Other carcinomas -(+)
- Mal. mesothelioma +/-



Serous carcinoma WT1

Ovarian serous carcinoma



“Liver cell markers”

Alpha fetoprotein

Hepatocyte antigen

Arginase

Glypican 3

canCD66a (biliary glycoprotein)

canCD10

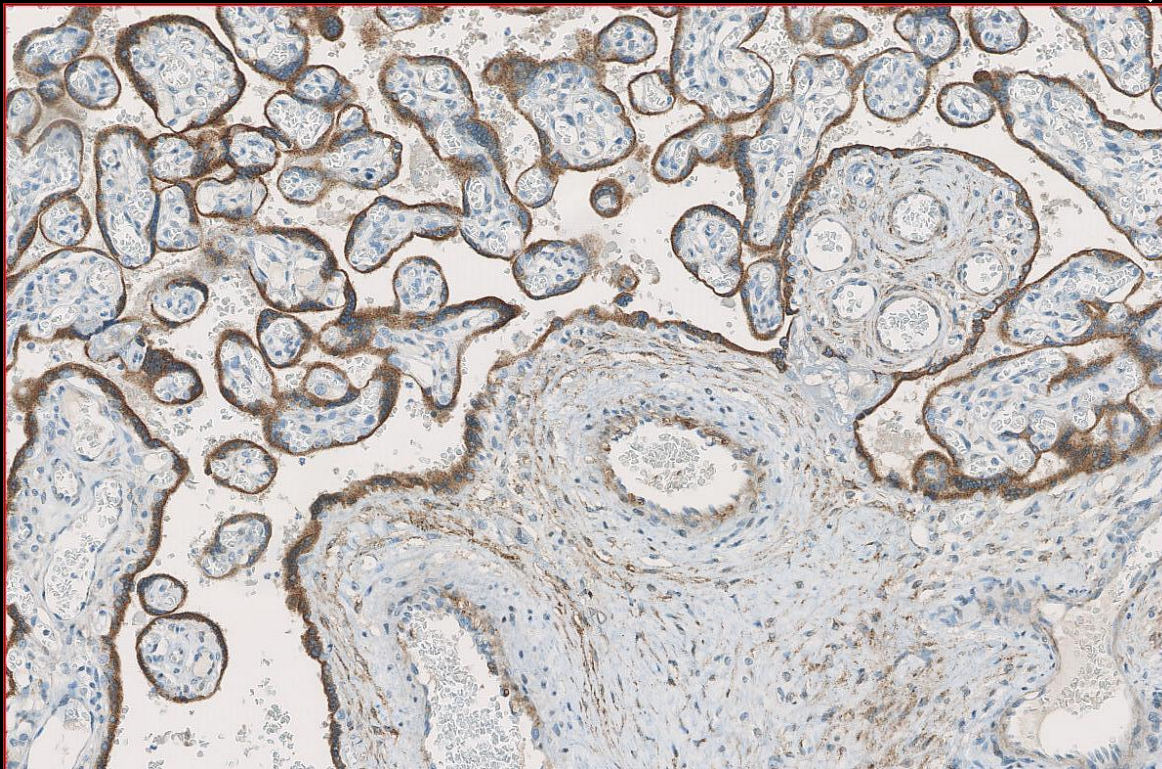
canVillin

Glutamine synthetase 6

Glypican 3

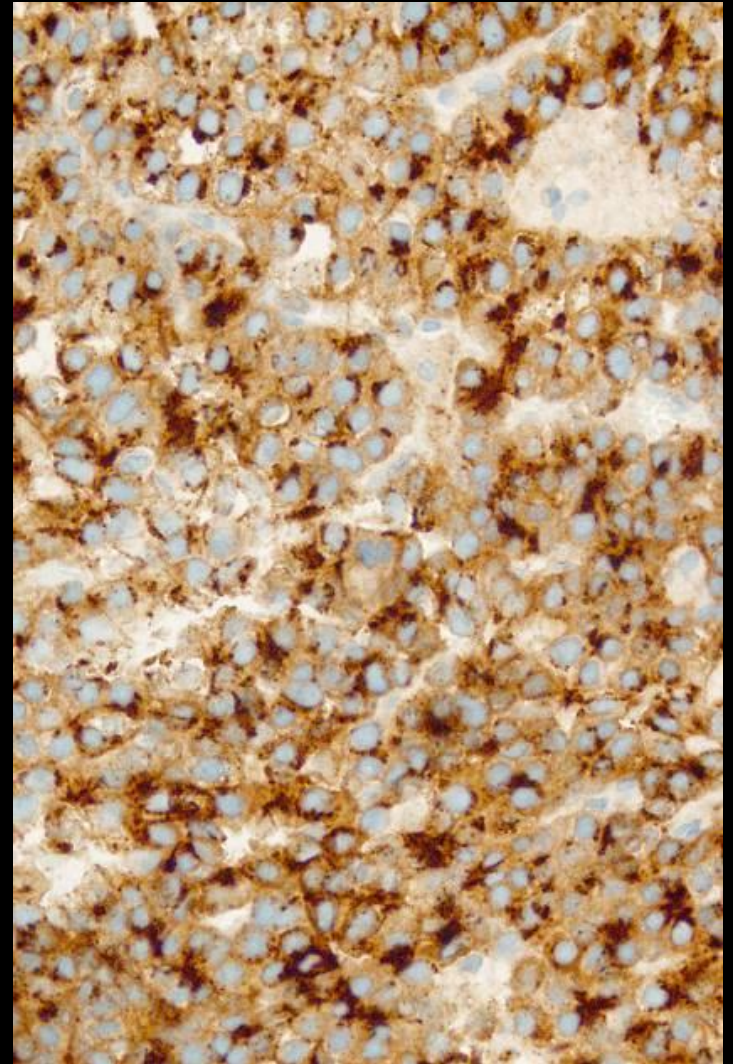
Cell surface heparan sulphate proteoglycan regulating cell growth and differentiation.

In normal tissues largely restricted to embryonic and foetal tissue and placental syncytiotrophoblast



Glypican 3

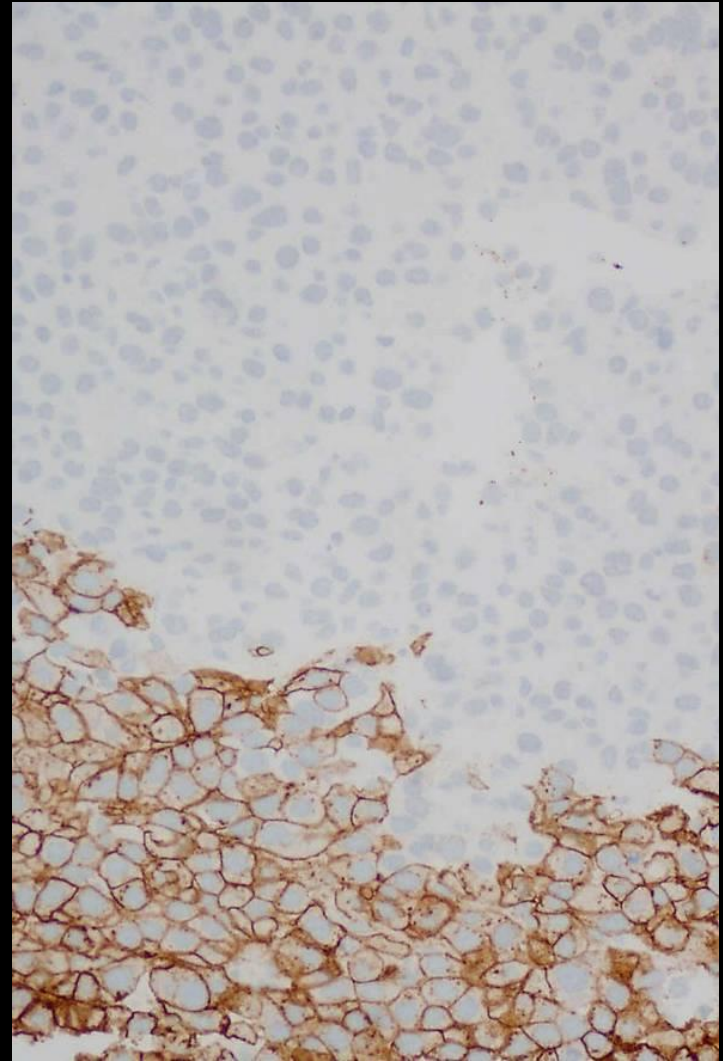
- Hepatocellular carcinoma +/-
- Yolk sac tumour +
- Chorionic carcinoma +
- Emb. carcinoma -(+)
- Colorectal adenocarcinoma +/-
- Gastric adenocarcinoma -/+
- Merkel cell carcinoma +/-
- Ovarian clear cell carcinoma -/+
- Ovarian serous carcinoma -(+)
- Liposarcoma +/-



HCC

Glypican 3

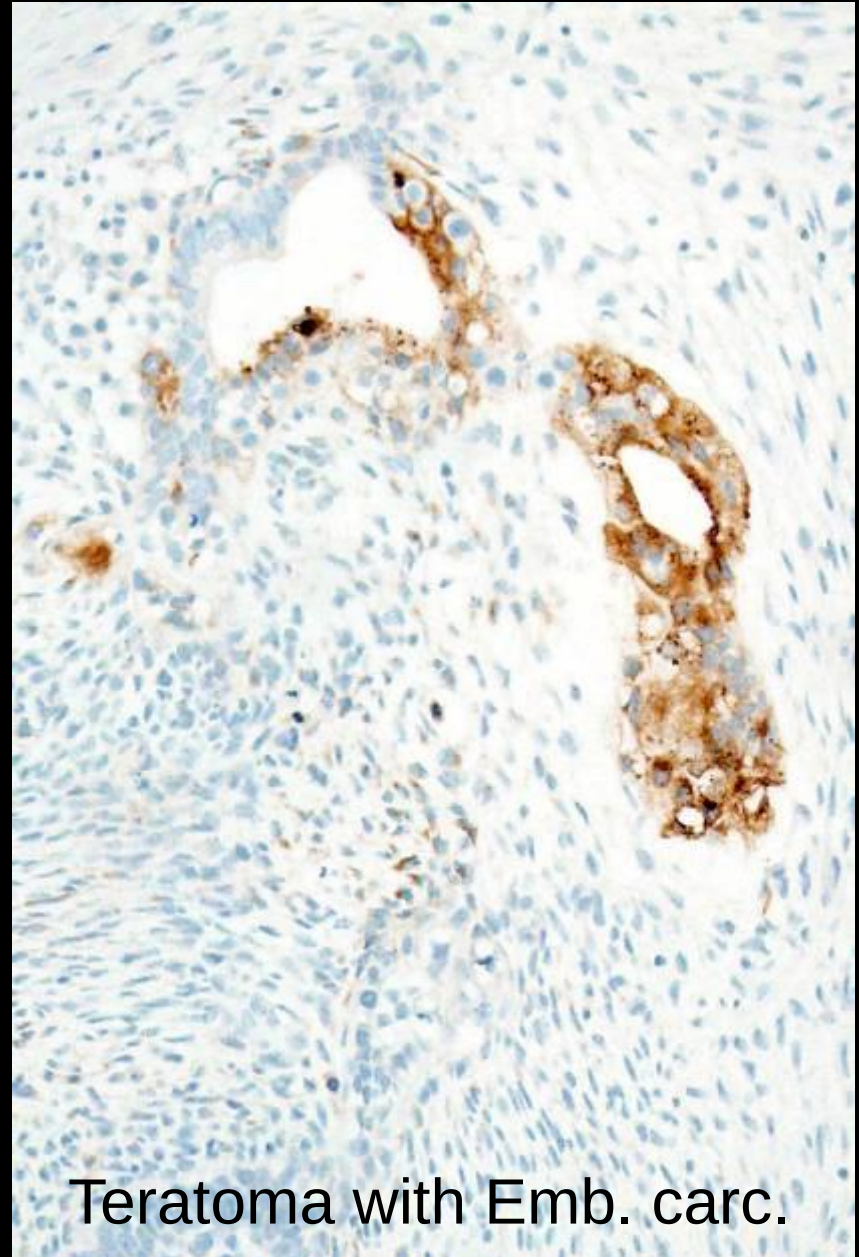
- Hepatocellular carcinoma +/- →
- Yolk sac tumour +
- Chorionic carcinoma +
- Emb. carcinoma -(+)
- Colorectal adenocarcinoma +/-
- Gastric adenocarcinoma -/+
- Merkel cell carcinoma +/-
- Ovarian clear cell carcinoma -/+
- Ovarian serous carcinoma -(+)
- Liposarcoma +/-



HCC

Glypican 3

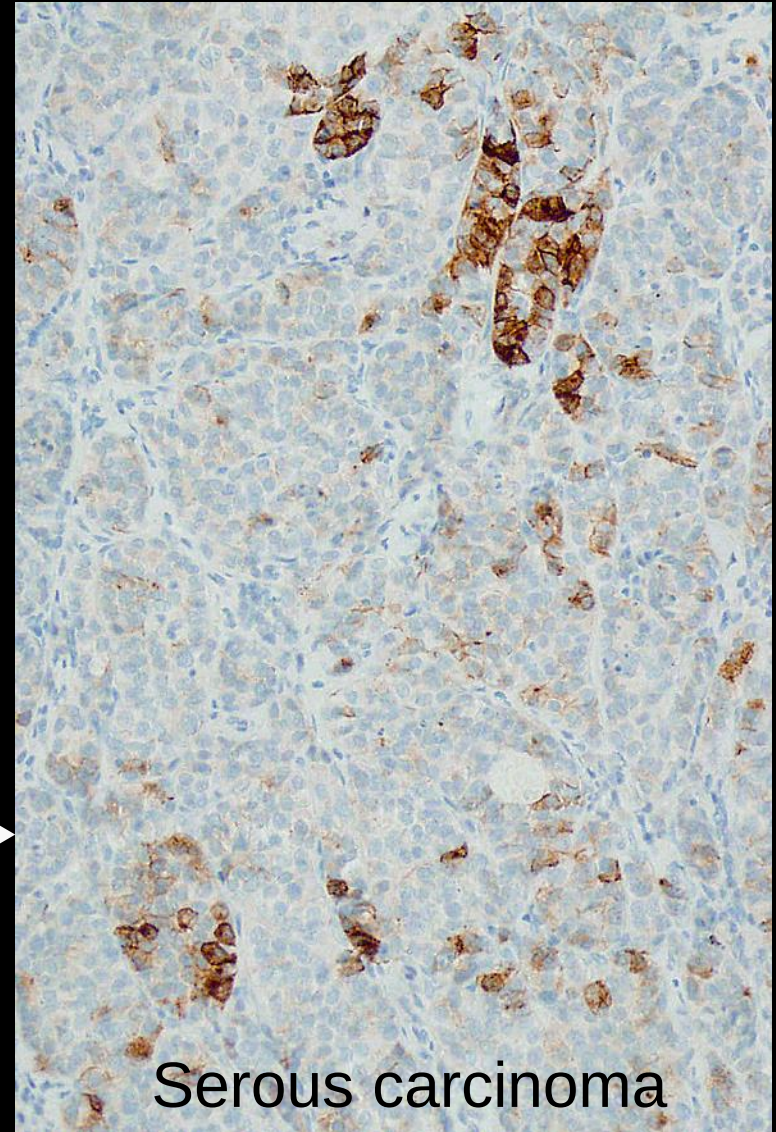
- Hepatocellular carcinoma +/-
- Yolk sac tumour +
- Chorionic carcinoma +
- Emb. carcinoma -(+)
- Colorectal adenocarcinoma +/-
- Gastric adenocarcinoma -/+
- Merkel cell carcinoma +/-
- Ovarian clear cell carcinoma -/+
- Ovarian serous carcinoma -(+)
- Liposarcoma +/-



Teratoma with Emb. carc.

Glypican 3

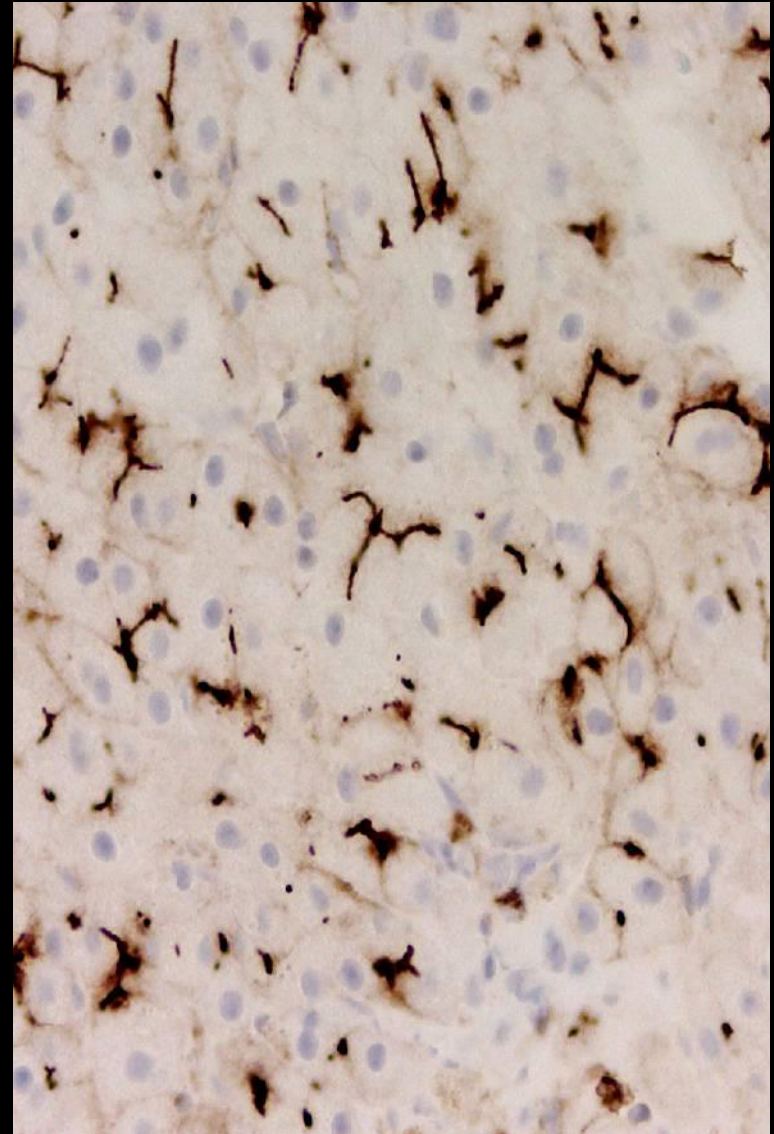
- Hepatocellular carcinoma +/-
- Yolk sac tumour +
- Chorionic carcinoma +
- Emb. carcinoma -(+)
- Colorectal adenocarcinoma +/-
- Gastric adenocarcinoma -/+
- Merkel cell carcinoma +/-
- Ovarian clear cell carcinoma -/+
- Ovarian serous carcinoma -(+) →
- Liposarcoma +/-



CD66a (biliary glycoprotein-1)

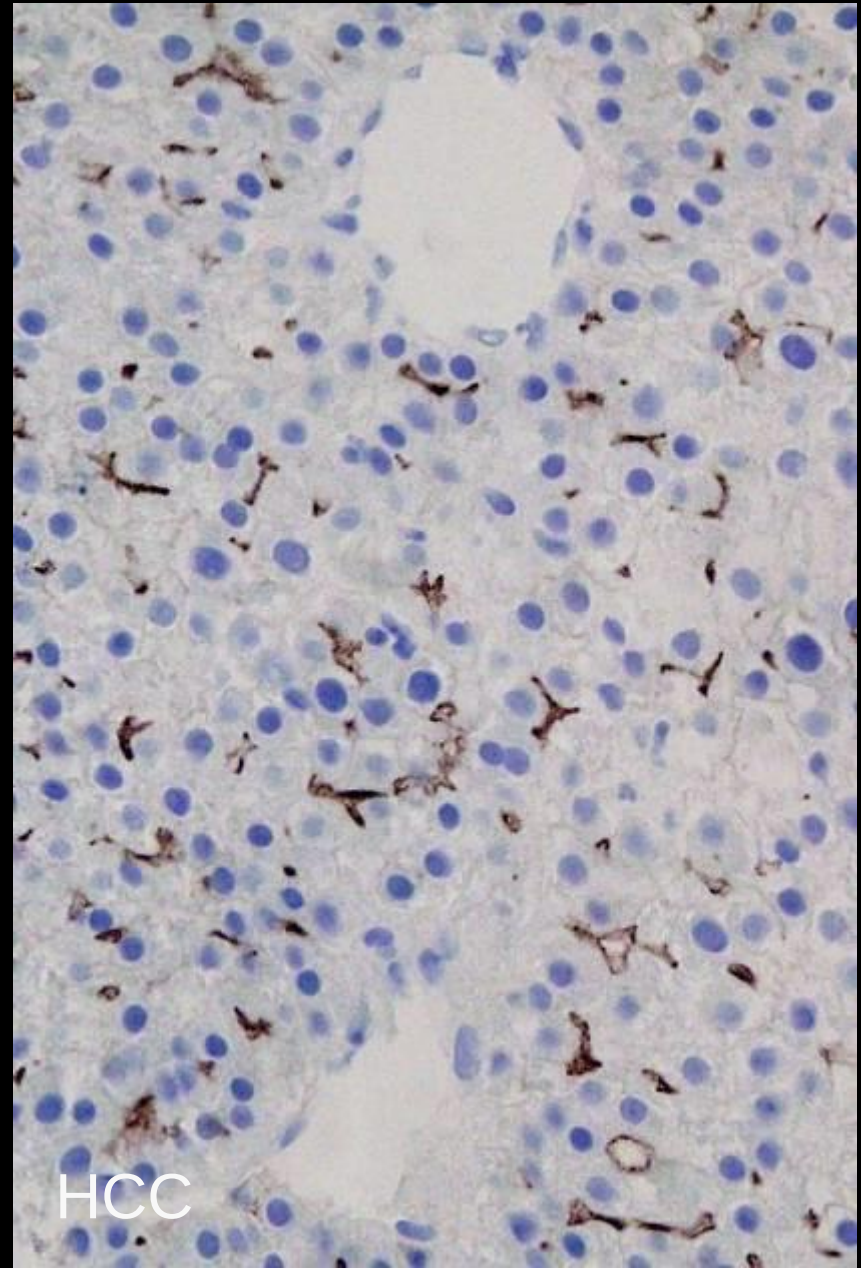
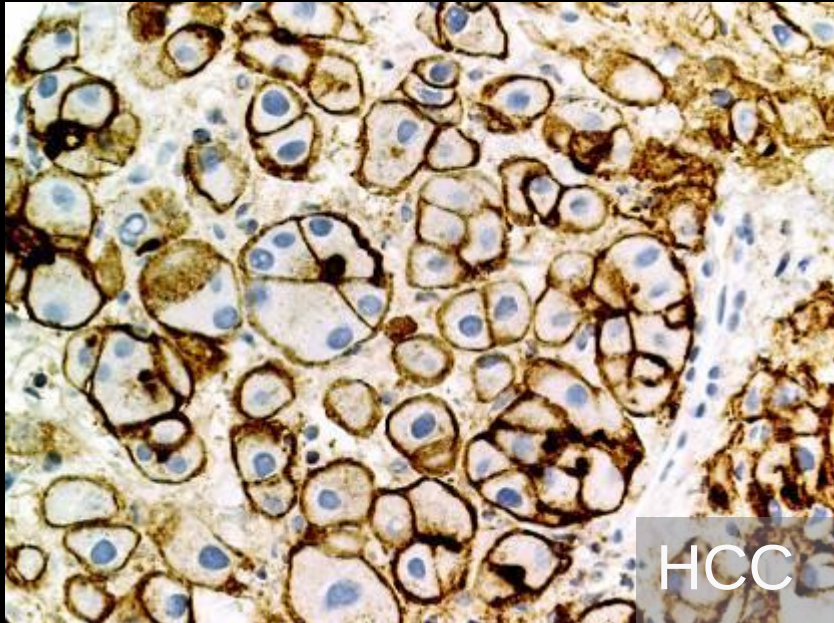
CEA-like cell adhesion molecule ("pCEA)

- Bile canaliculi
- Many epithelia
- Trophoblast

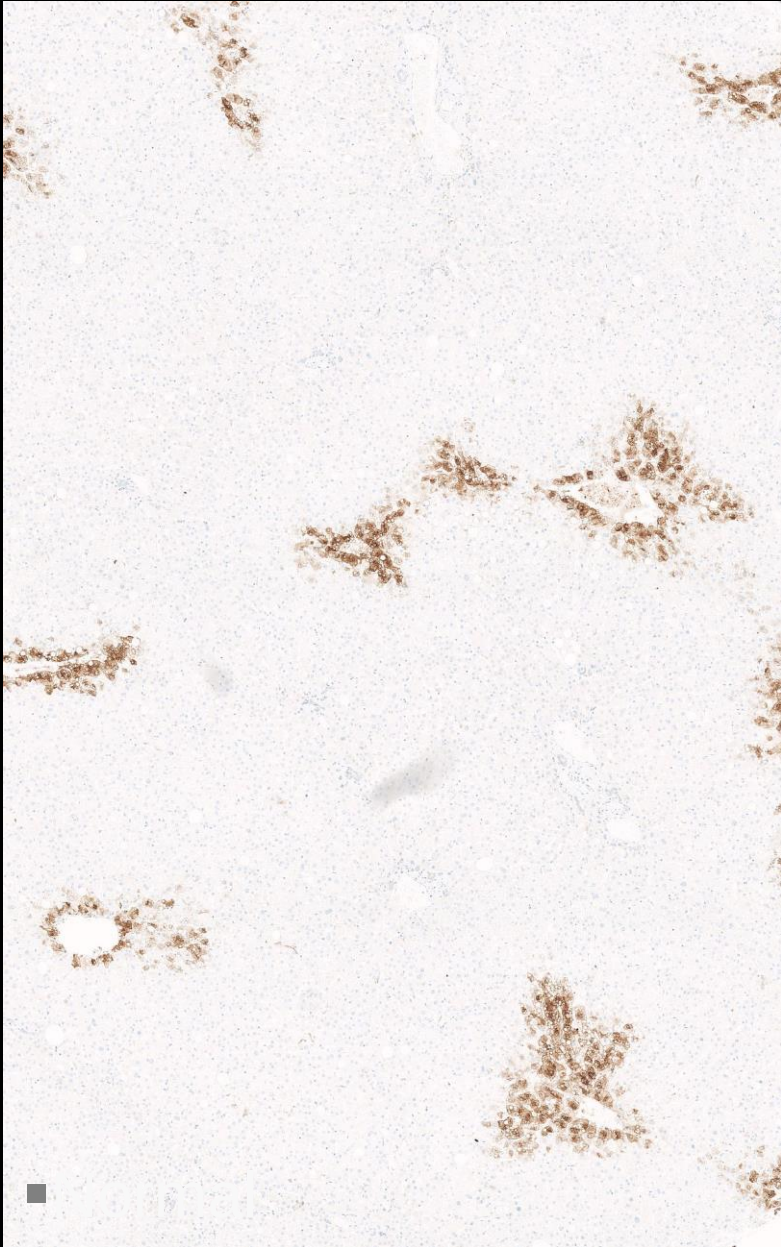


canCD66a (biliary glycoprotein-1)

Hepatocellular carcinoma
~70% canalicular staining

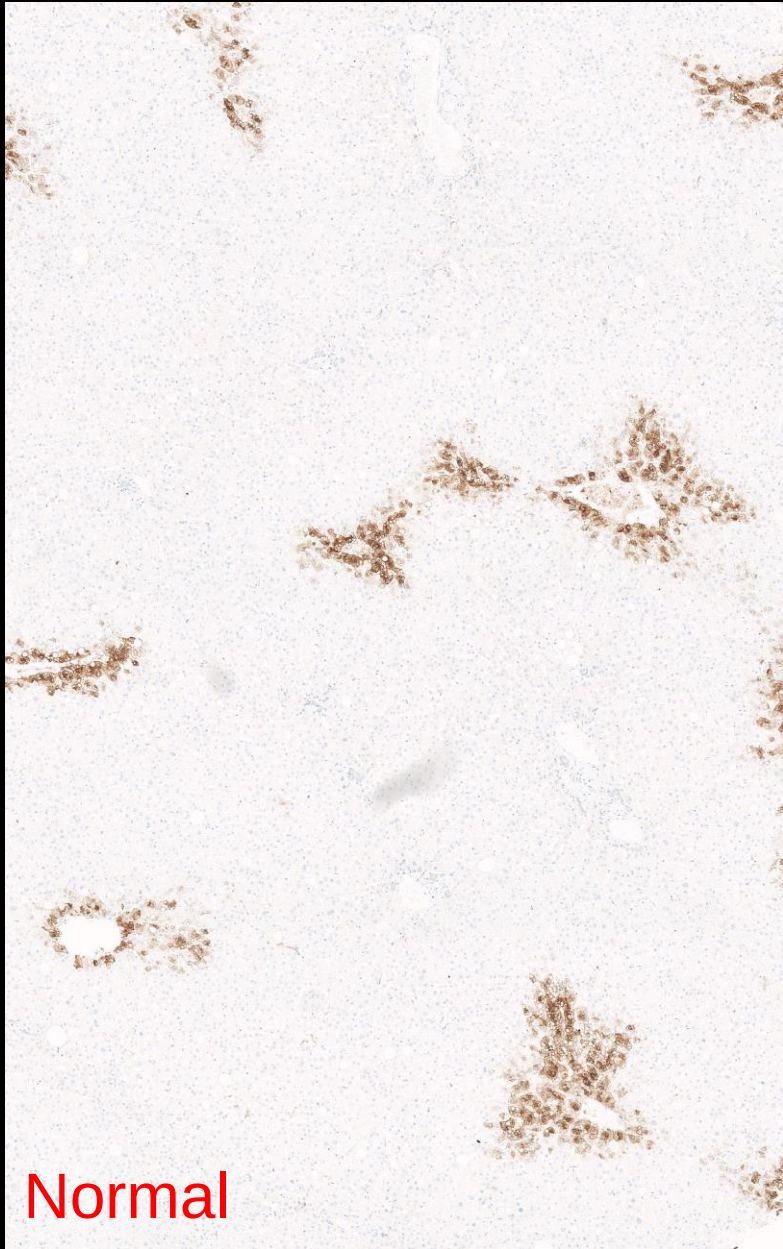


Glutamine synthetase in liver

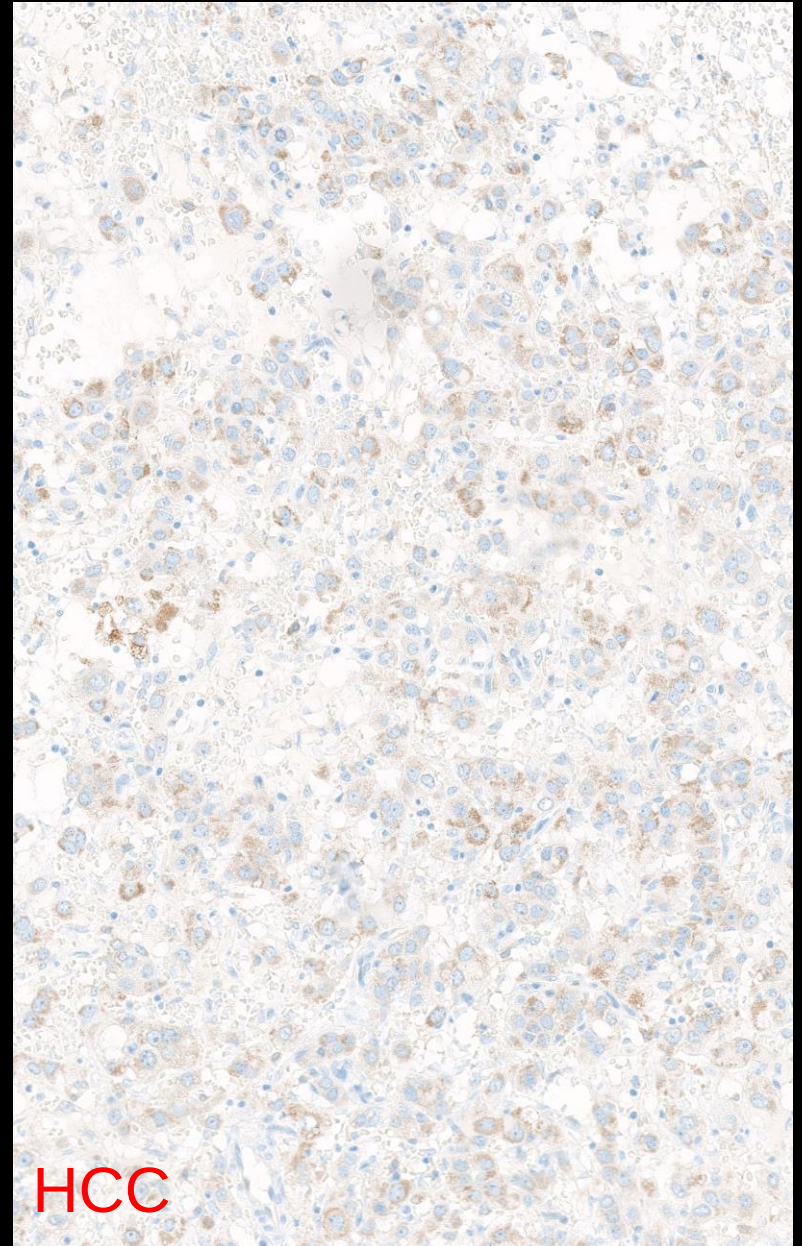
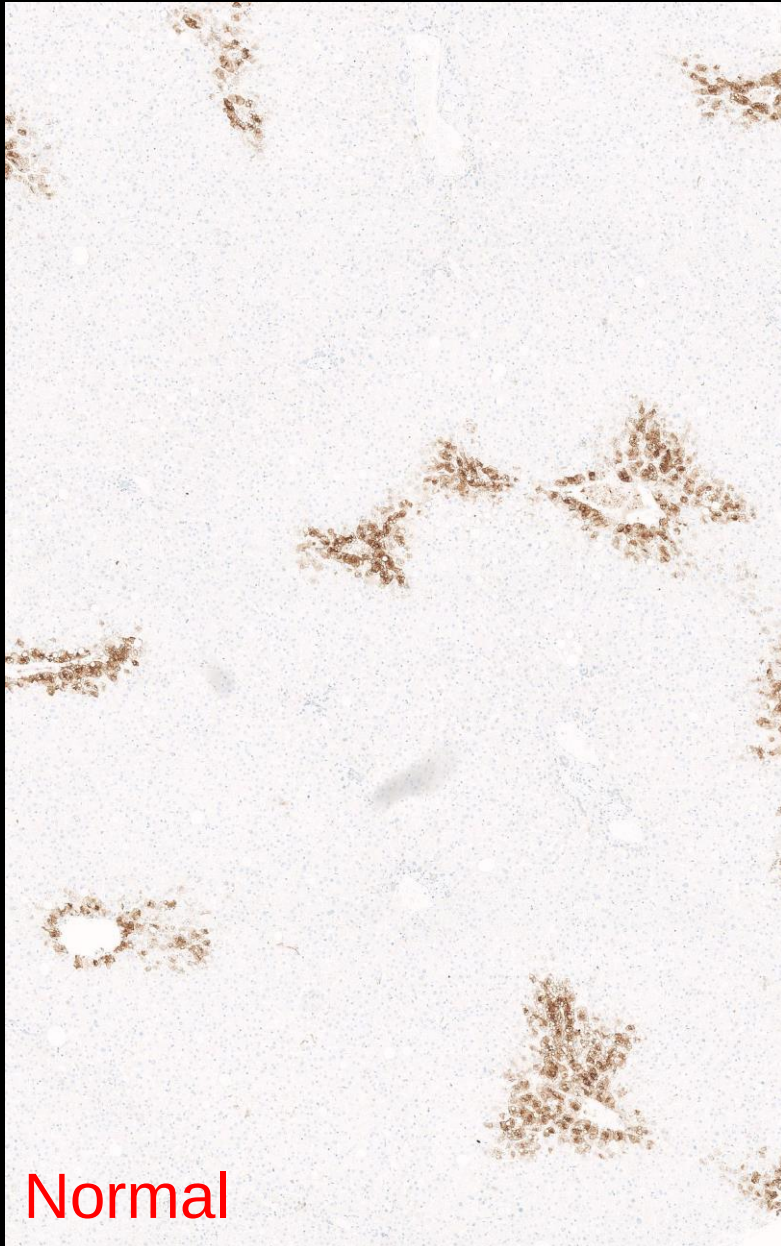


- GS: Member of an enzyme family that catalyzes the synthesis of glutamine from glutamate and ammonia.
- It plays an important role in ammonia detoxification, nitrogen balance and pH regulation in the liver

Glutamine synthetase in liver



- Glutamine synthetase in liver



Neuroendocrine cell markers

Synaptophysin

Chromogranin

Hormones

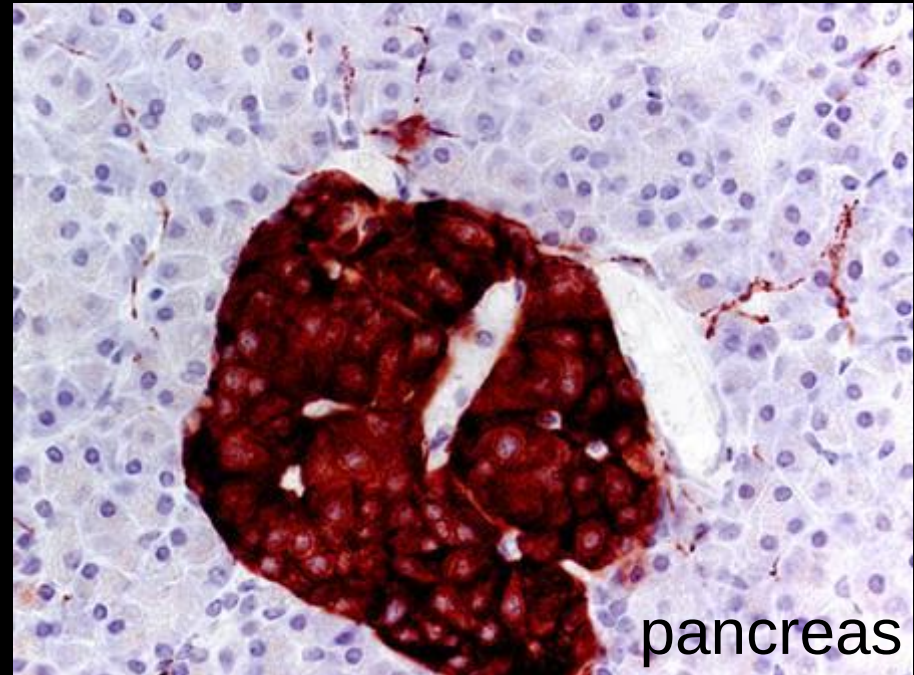
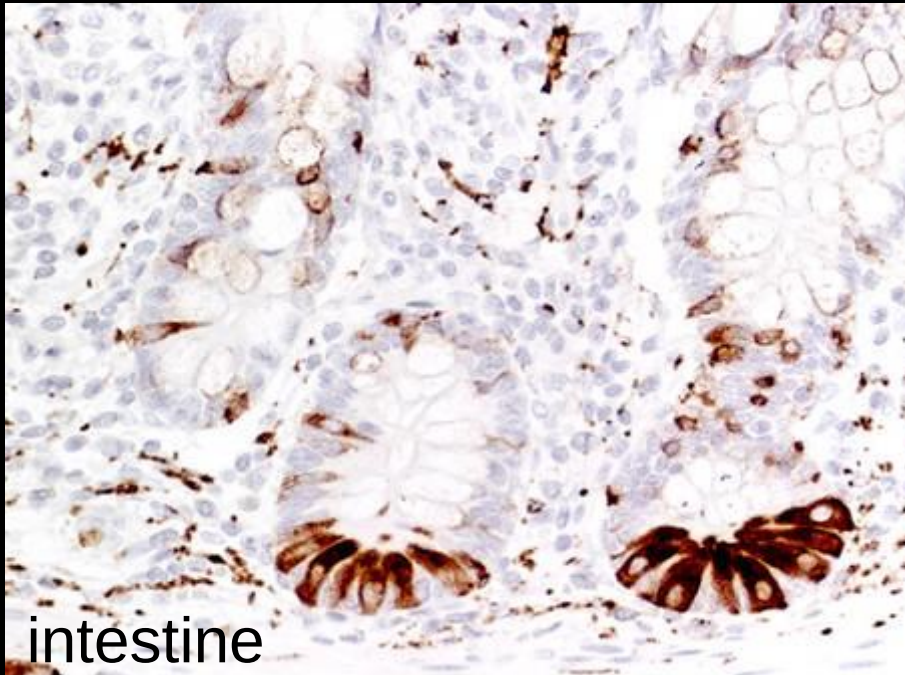
(CD56)

(NSE)

(GPG9.5)

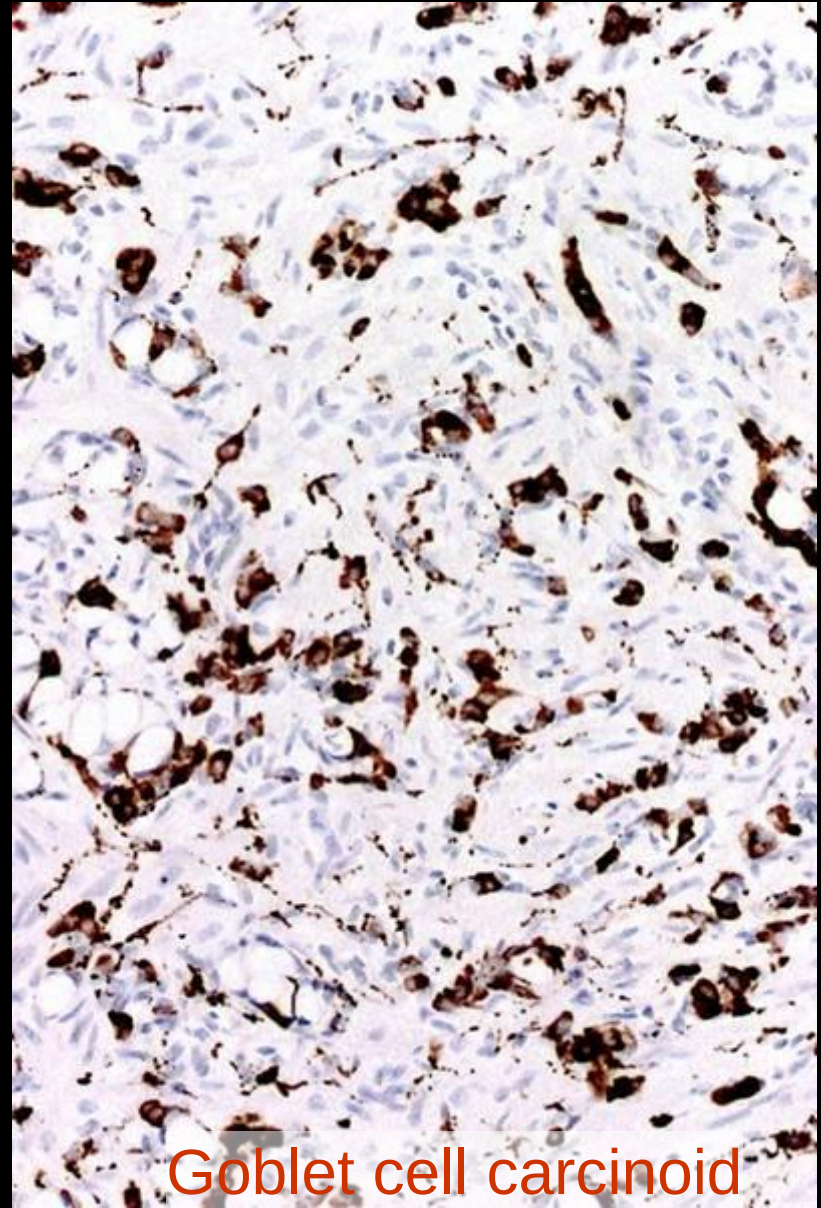
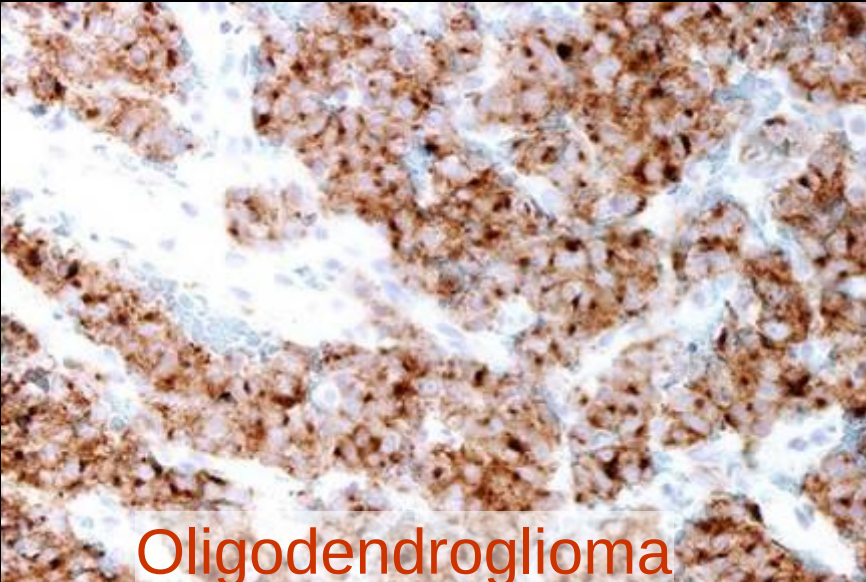
Synaptophysin

- An integral-membrane glycoprotein of presynaptic vesicles
- Neurons
- Neuroendocrine cells
- (Adrenal cortical cells)

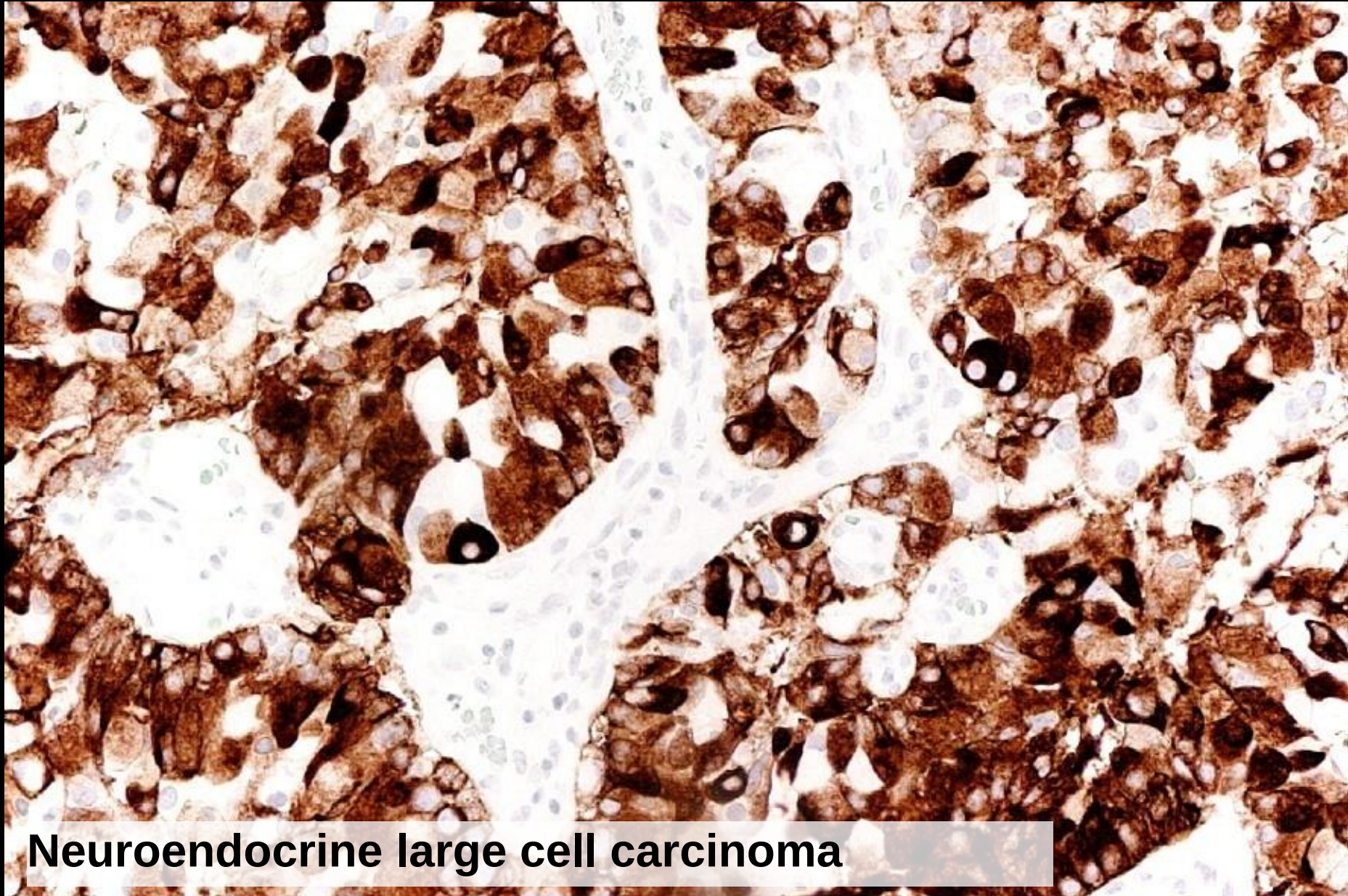


Synaptophysin in neoplasias

- Neuronal neoplasms
- Neuroendocrine neopl.
 - carcinoid/neuroendocr. carc.
 - pancreatic islet tumours
 - medullary thyroid carcinoma
 - pituitary & parathyroid ad.
- Adrenal cortical tumours



Synaptophysin in endocrine tumours



Neuroendocrine large cell carcinoma

Synaptophysin in neoplasias

