

NordiQC Workshop in Diagnostic Immunohistochemistry

Culture & Congress Centre

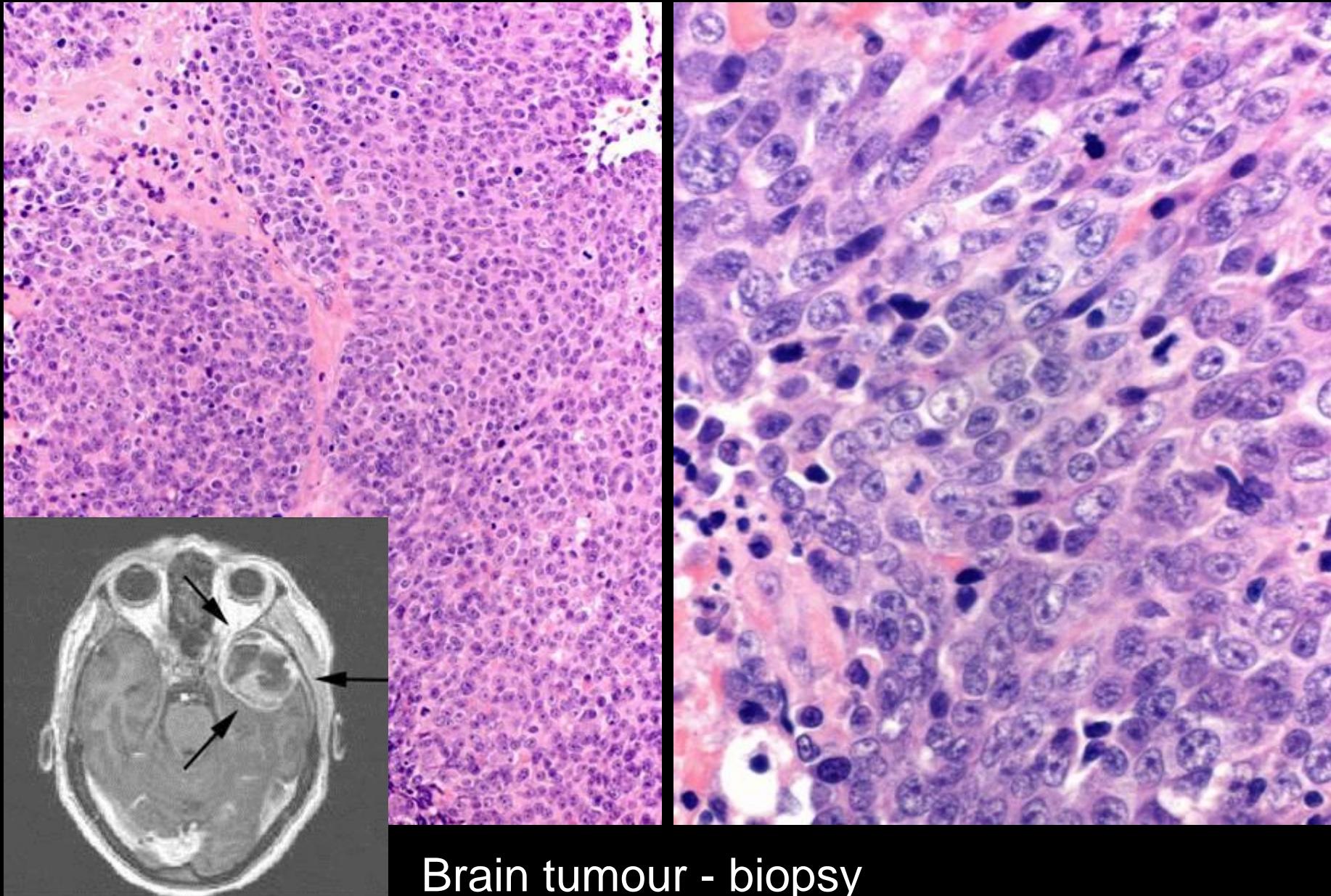
2nd – 4th October 2019



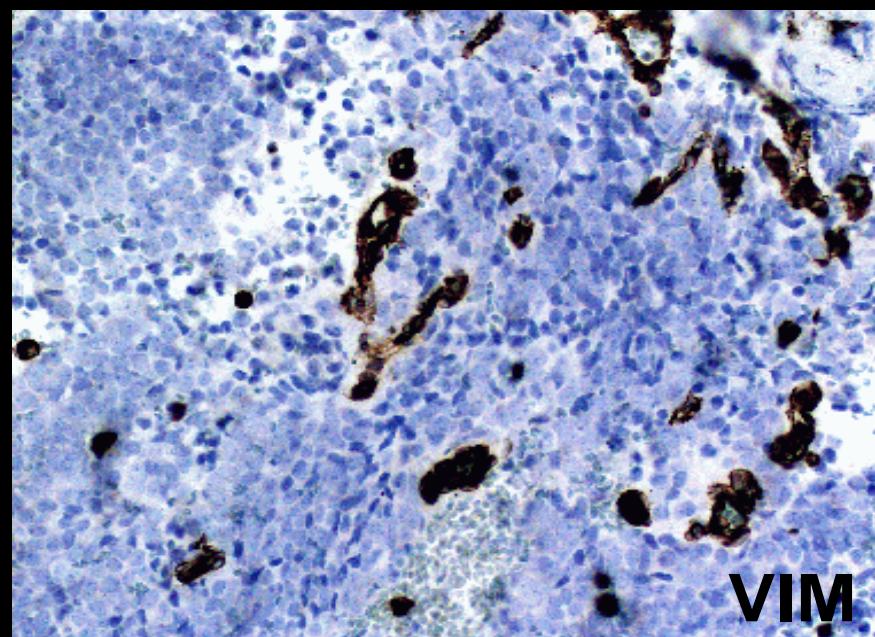
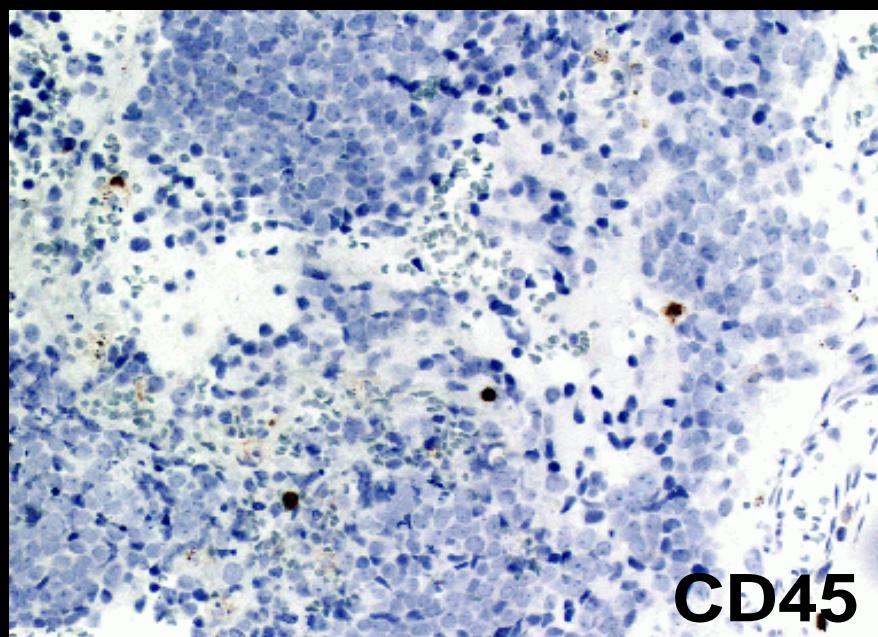
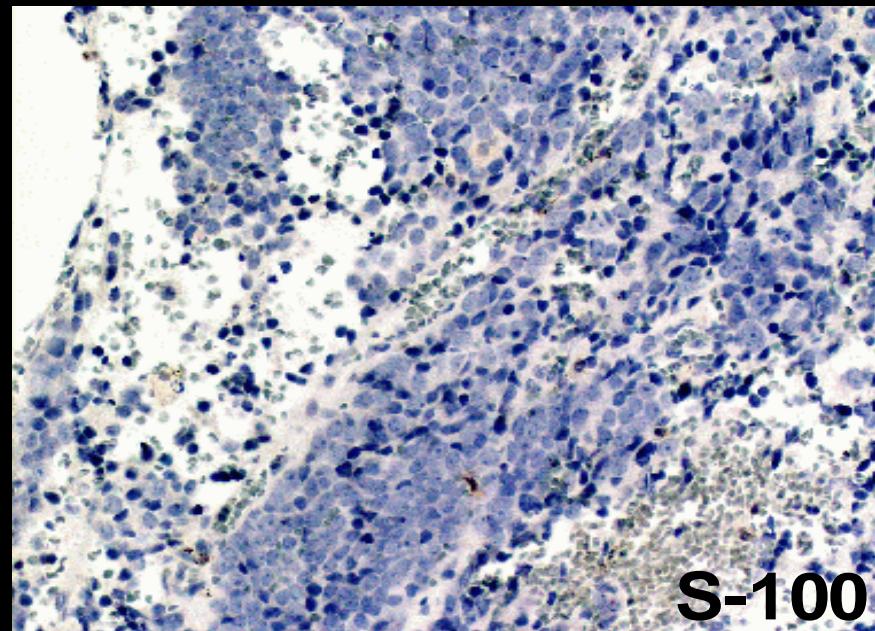
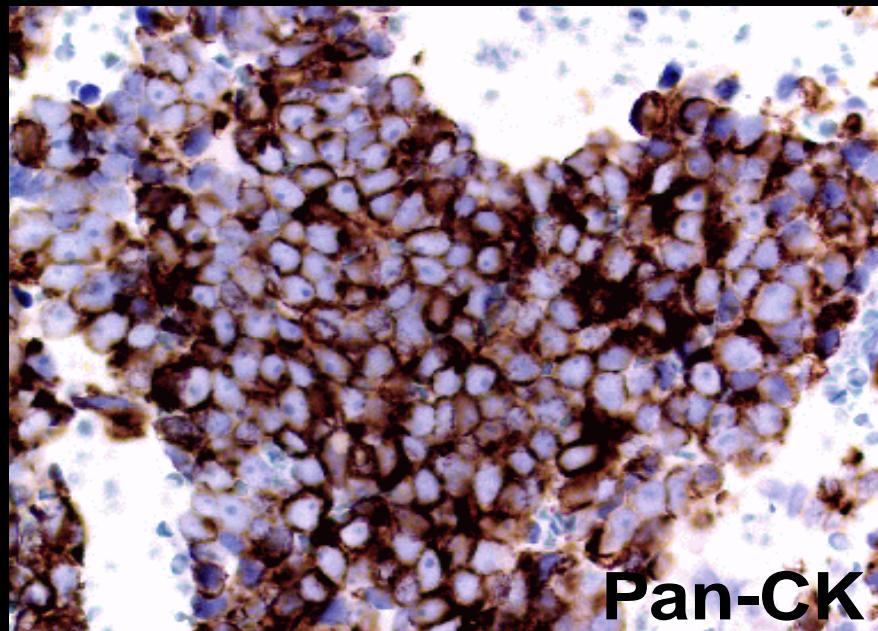
AALBORG UNIVERSITY HOSPITAL

The unknown primary

Tumours of unknown origin: Histology



Tumours of unknown origin: Immunohistochemistry



IHC classification of the Unknown Primary Tumour

UPT: A tumour appearing in metastatic setting without a histologically proven primary tumour.

UPT pose an increasing challenge for the pathologist - due to the progress in surgical and oncological treatment possibilities.

IHC classification of the Unknown Primary Tumour

New, relatively specific antibodies give the pathologist more and better diagnostic tools.

But the diagnostic work also become more complex in terms of planning, optimization of protocols, interpretation of reaction patterns and error trapping.

IHC classification of the Unknown Primary Tumour

10 - 15% of cancers remained UPTs

+ ??% uncertain if primary or metastatic

- liver, lung, bone, lymph nodes, brain, peritoneum . . .

‘Undifferentiated’ neoplasms (5-10%)

- carcinomas, sarcomas, melanomas, germ cell tumours
- malignant lymphomas

- Adenocarcinomas (80-90%)

- lung, breast, prostate, colorectum, ovary, pancreas ...

- Squamous cell carcinomas (5-10%)

- lung, esophagus, uterine cervix ...

IHC classification of the Unknown Primary Tumour

Differences in prognosis

Differences in treatment regimes

- malignant lymphomas

- carcinomas (breast, prostate, ovary . . .)

- sarcomas (GIST, synovial sarcoma . . .)

- germ cell tumours

Pathology tests cost effective

Pathology tests save patient discomfort

The patient's 'right to know'

The risk of hereditary cancer

IHC classification of the Unknown Primary Tumour

- Most likely diagnoses
- Relevant differential diagnoses
 - ↓
- Optimal selection of antibodies for a diagnostic algorithm
 - Primary and secondary antibody panels
 - Turn-around-time
 - Laboratory expenses

IHC classification of the Unknown Primary Tumour

Pathologist

- knowledge, acceptance, skill

Tumour material

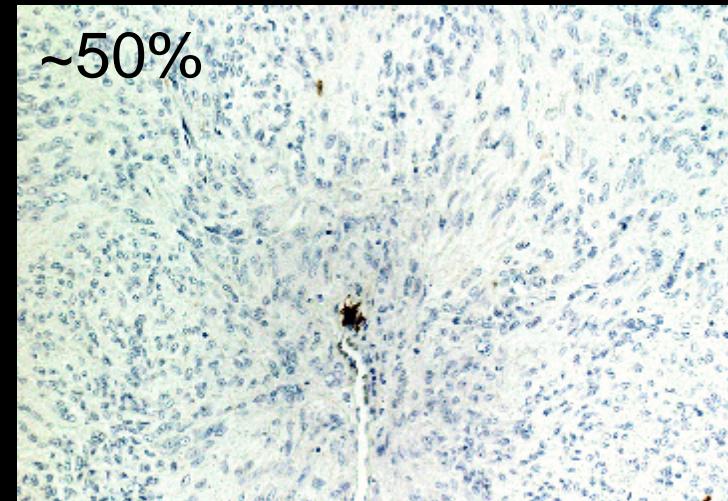
- diagnostic markers

Antibodies available

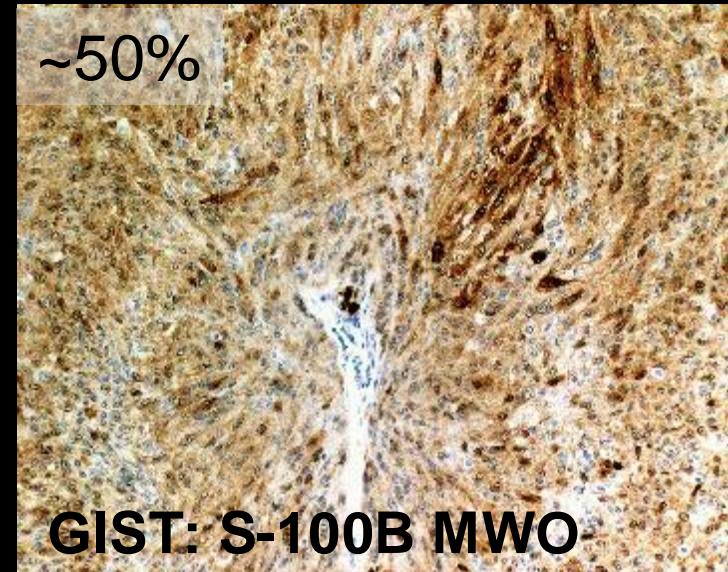
- applic. in diagnostic algorithms

Methods

- protocol:
sensitivity, specificity, reliability
- interpretation:
cut-off level for positivity
clinical relevance



GIST: S-100B Protease



GIST: S-100B MWO

IHC classification of the Unknown Primary Tumour

Pathologist

- knowledge, acceptance, skill

Tumour material

- diagnostic markers

Antibodies available

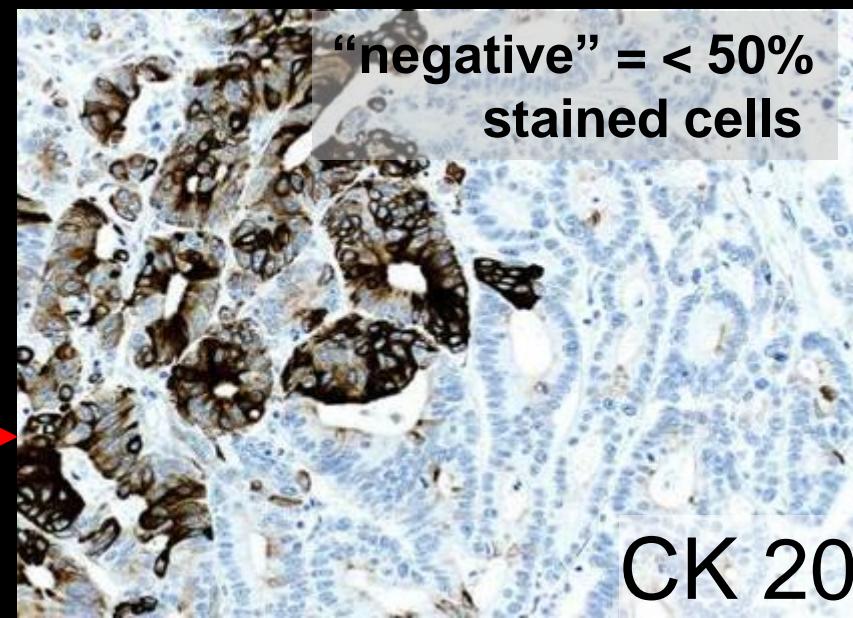
- applic. in diagnostic algorithms

Methods

- protocol:
sensitivity, specificity, reliability
- interpretation:
cut-off level for positivity
→ clinical relevance



CK 20



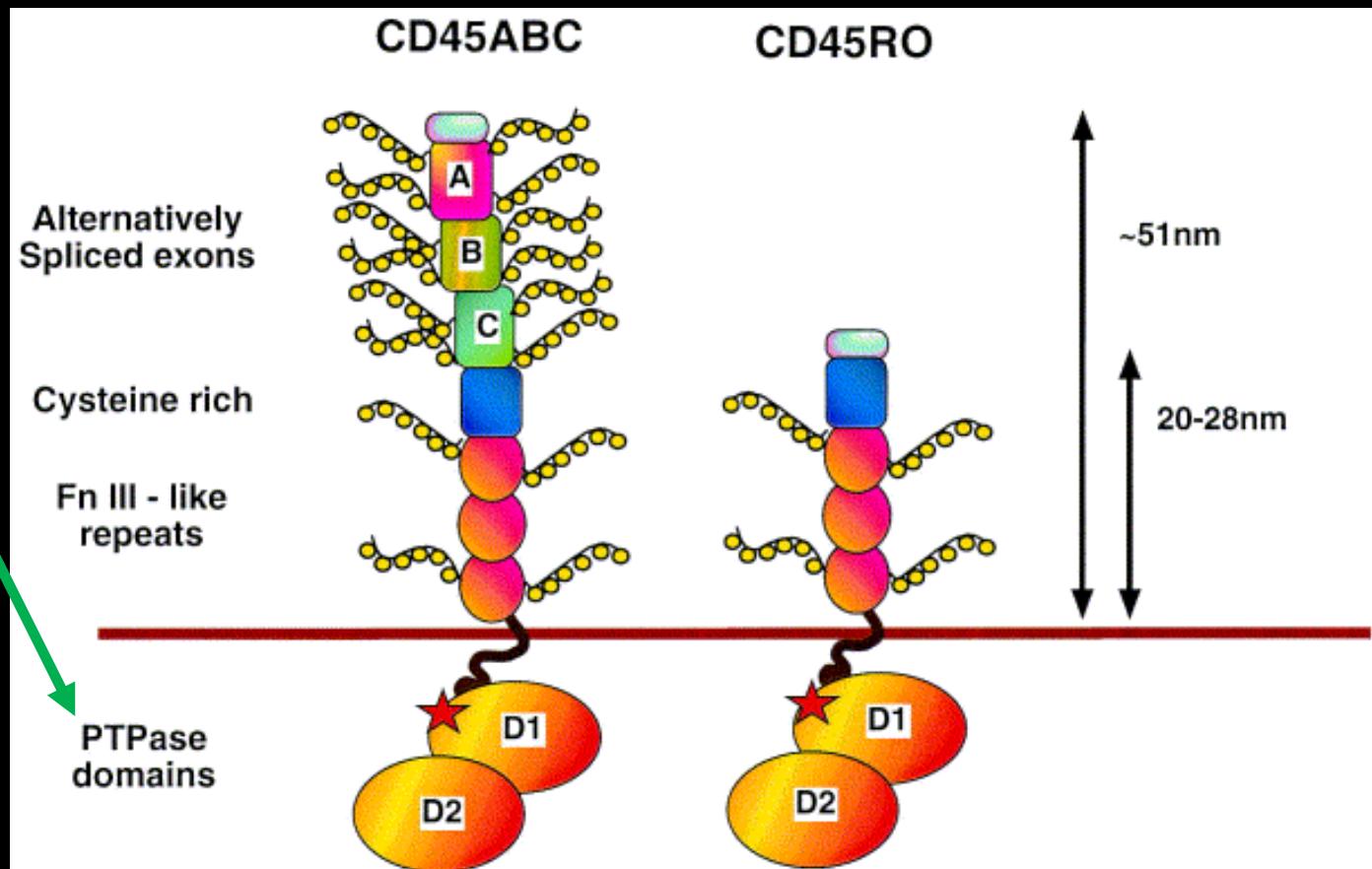
CK 20

Primary panel for the unknown primary tumour

	CD45	Pan-CK	S-100	VIM
Haemato-lymphoid neoplasms	+/-	-/(+)	-/(+)	+/-
Epithelial neoplasms	-	+/-	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

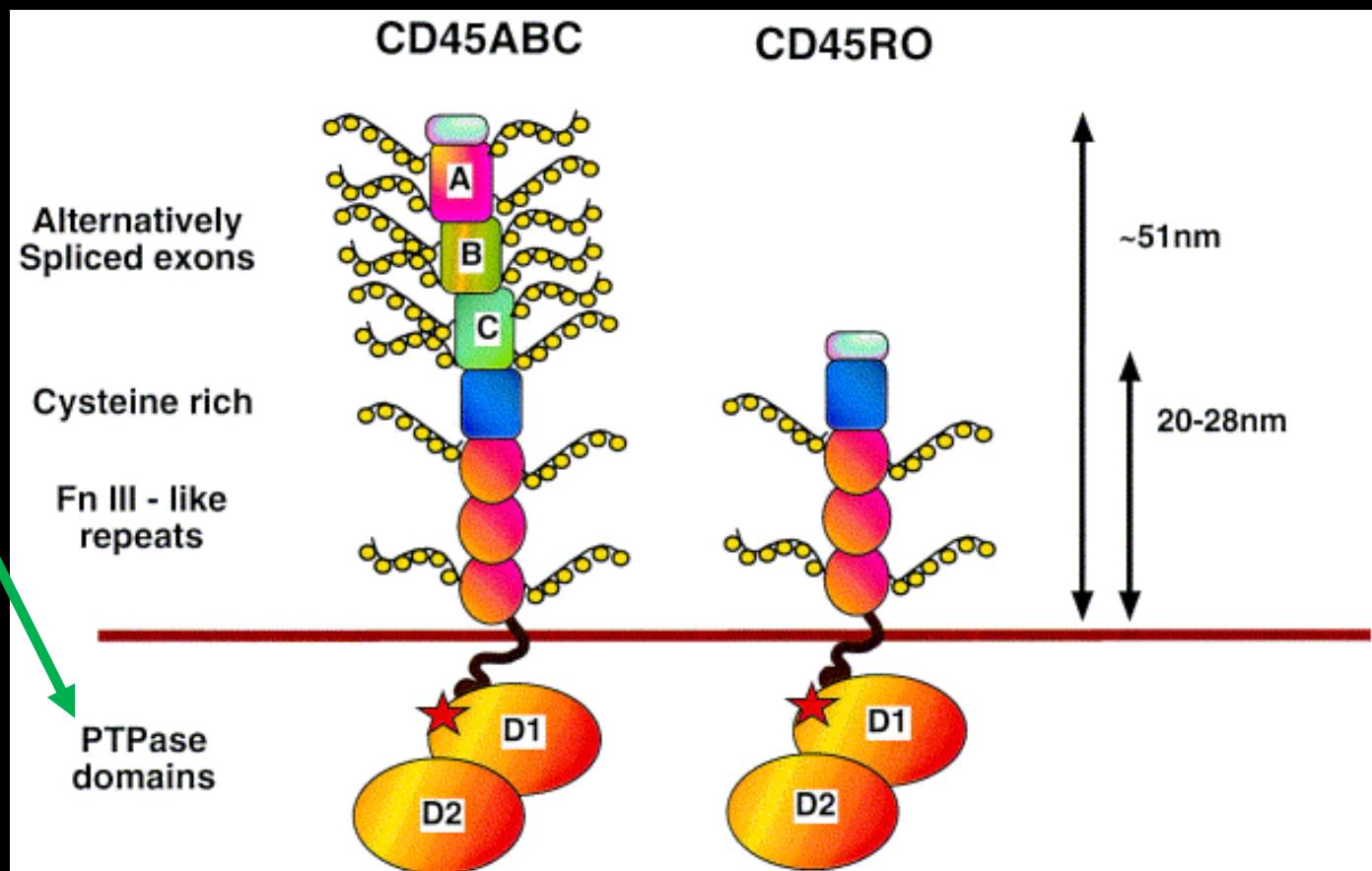
CD45 - Leucocyte common antigen (LCA)

- Transmembrane protein tyrosin phosphatase essential for **haematopoietic signal transduction and cell activation**
- Membrane associated component: 5 isotypes
- Intracellular component: one common type

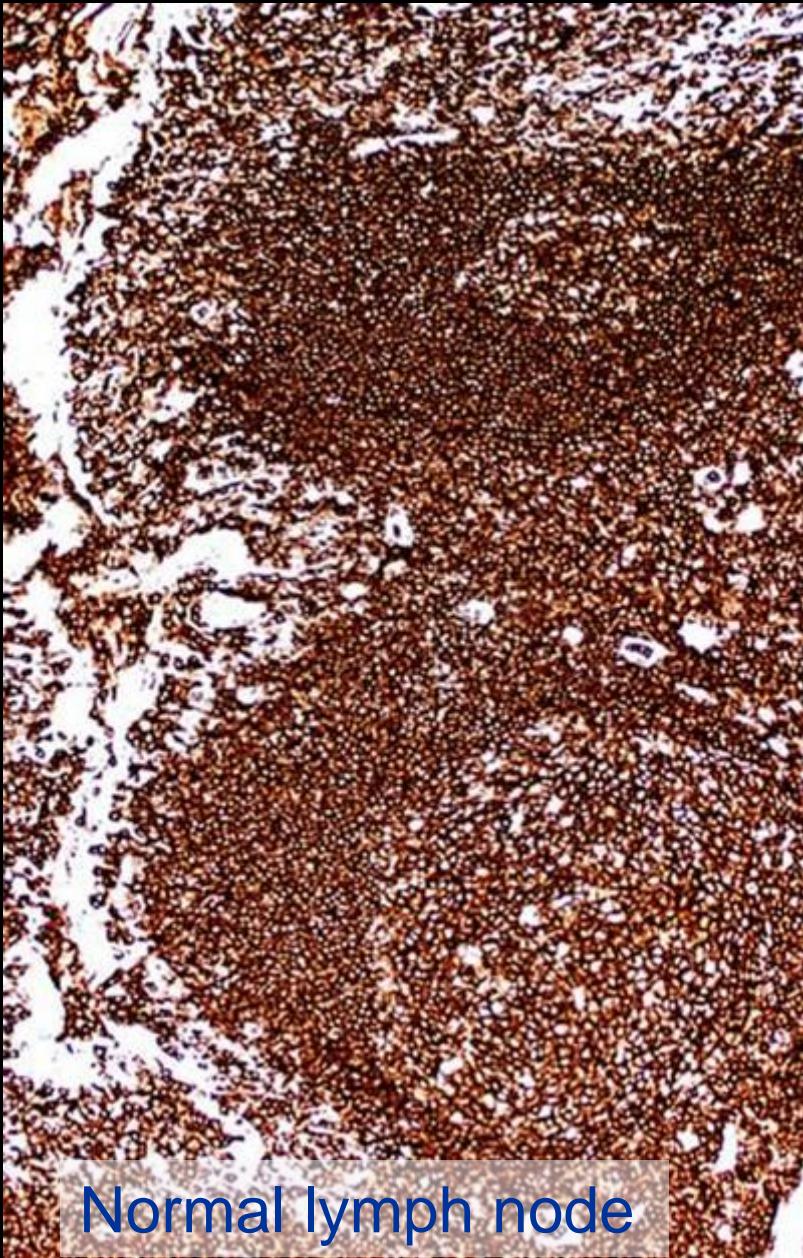


CD45 - Leucocyte common antigen (LCA)

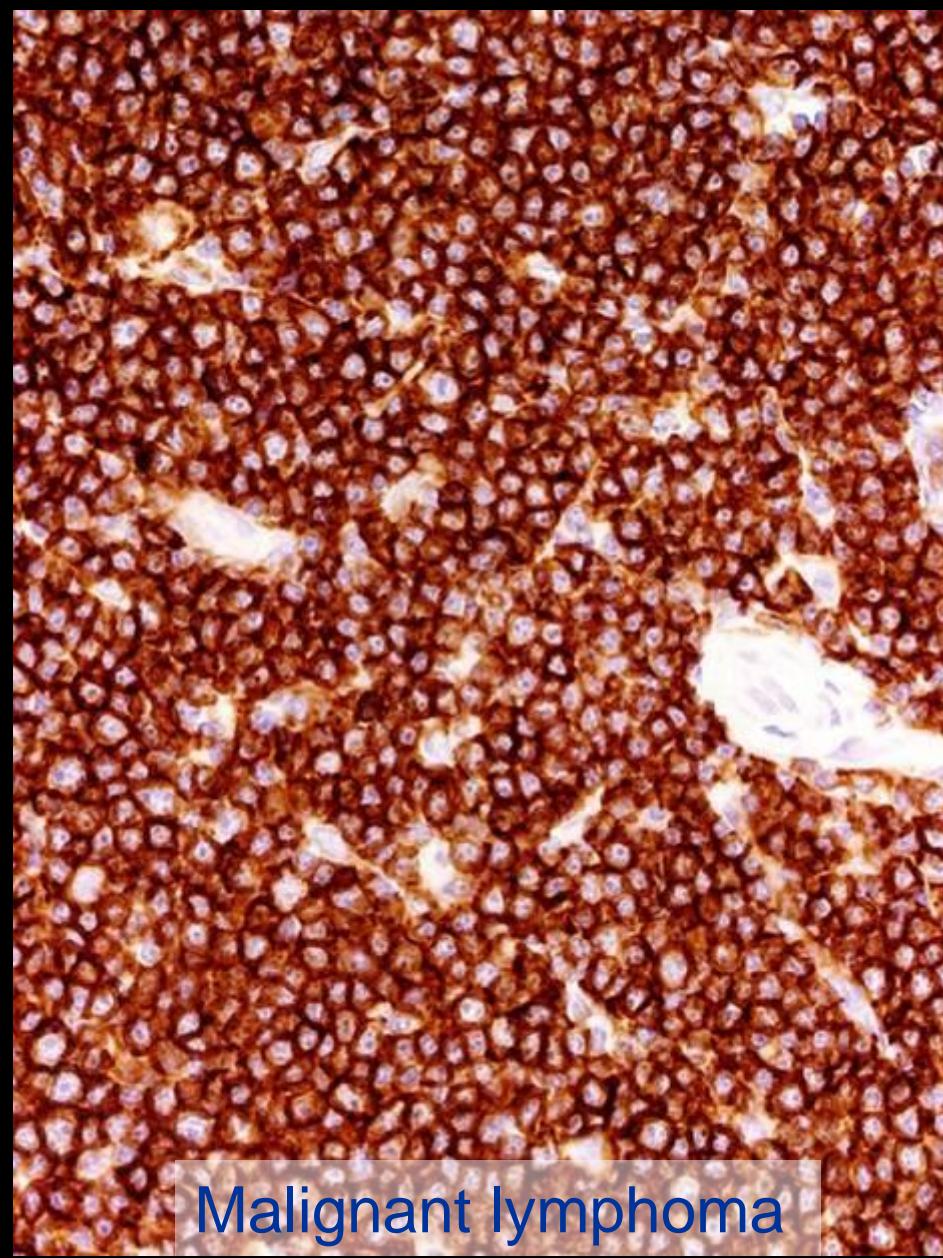
- Large majority of haematolymphoid cells and neoplasms
- Lost in *maturing erythrocytes, megakaryocytes and plasmacells*
- "Never" found in non-haematolymphoid cells and neoplasms



CD45 - Leucocyte common antigen (LCA)



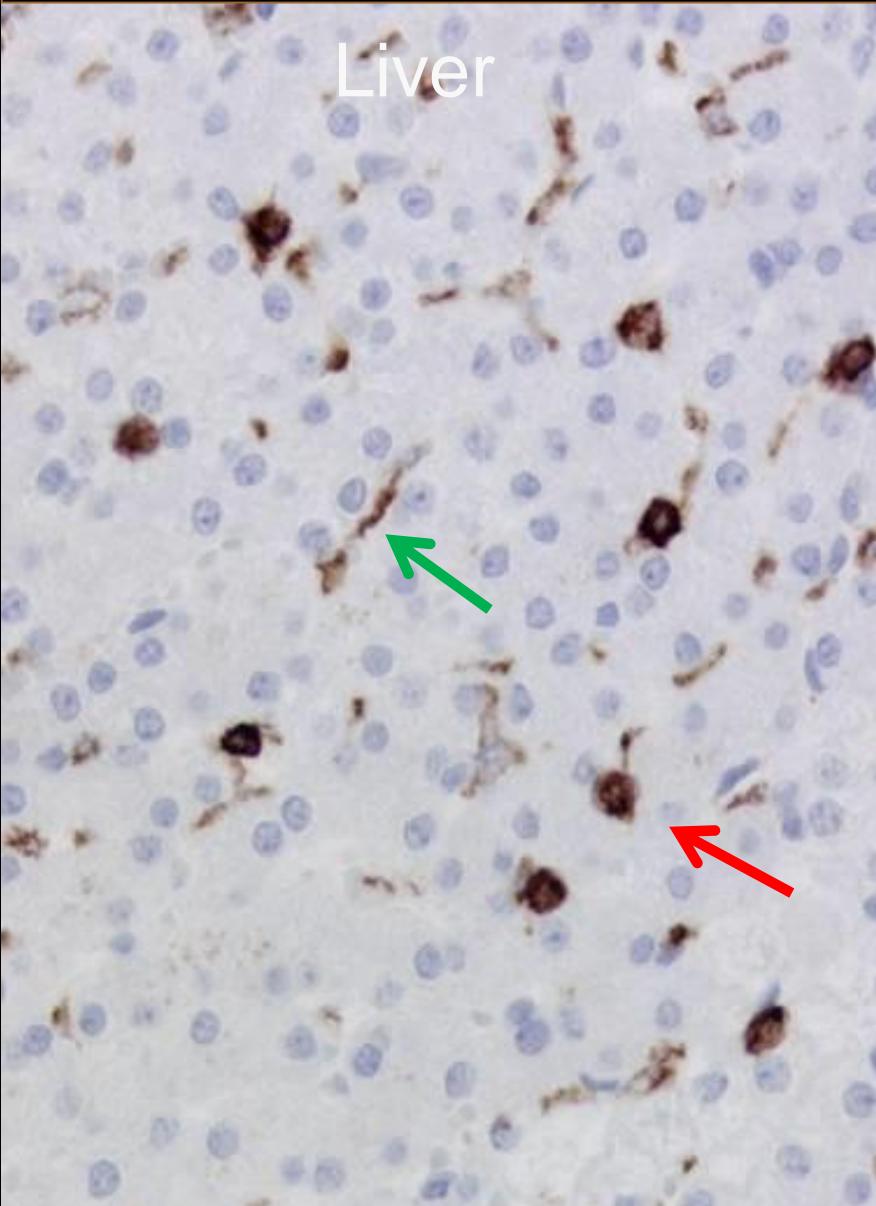
Normal lymph node



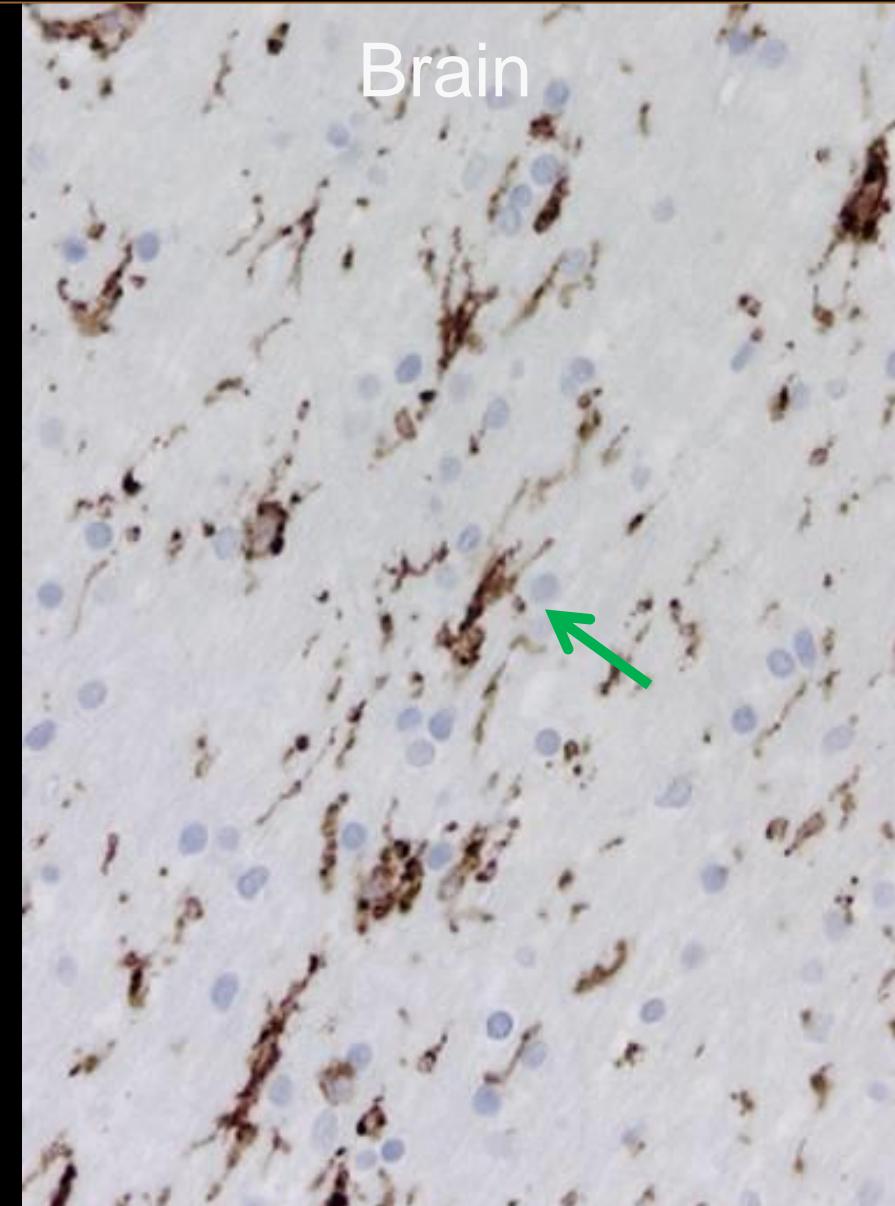
Malignant lymphoma

CD45 - Leucocyte common antigen (LCA)

Liver



Brain

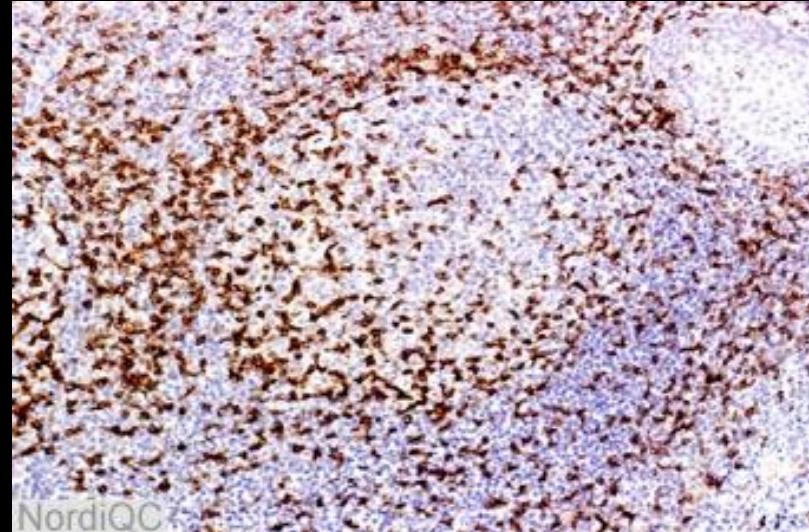


Kupffer cells: Critical assay performance control

CD45 - Leucocyte common antigen (LCA)



Lymph node/Tonsil



- CD45 RO ~ T-cells



- CD45 RA ~ B-cells

Cytokeratin-Positive, CD45-Negative Primary Centroblastic Lymphoma of the Adrenal Gland A Potential for a Diagnostic Pitfall

Ludvik R. Donner, MD, PhD; Frank E. Mott, MD; Isaac Tafur, MD

- We report a case of cytokeratin-positive, CD45-negative primary polymorphic centroblastic lymphoma of the adrenal gland. Additional immunostaining, which demonstrated positivity for CD20 and κ light chain, as well as detection of the monoclonal rearrangement of the immunoglobulin heavy chain gene, helped to establish the diagnosis of lymphoma and to rule out an initially favored diagnosis of poorly differentiated carcinoma.

(*Arch Pathol Lab Med*. 2001;125:1104–1106)

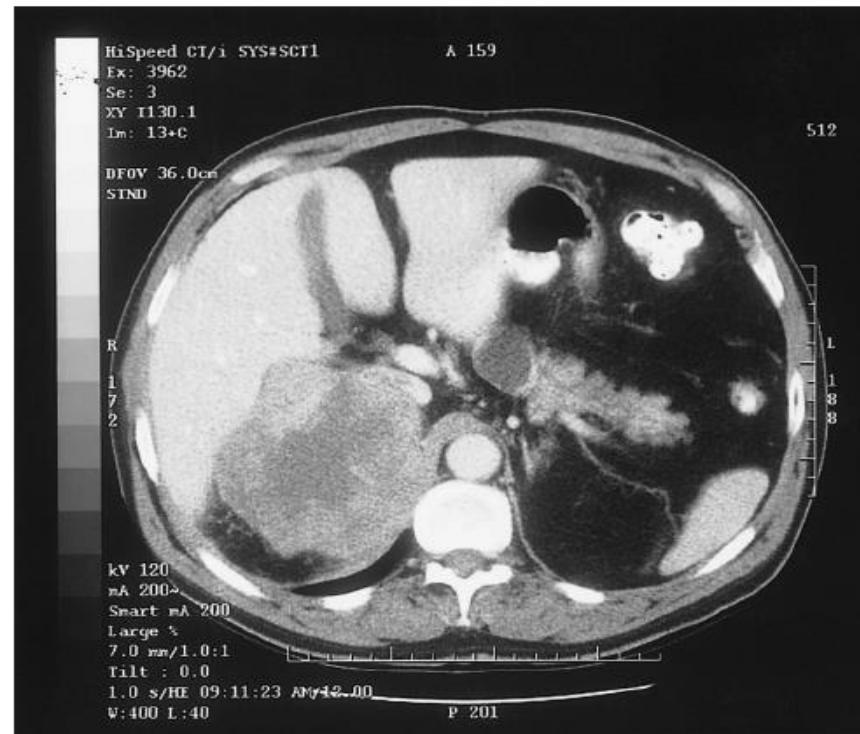
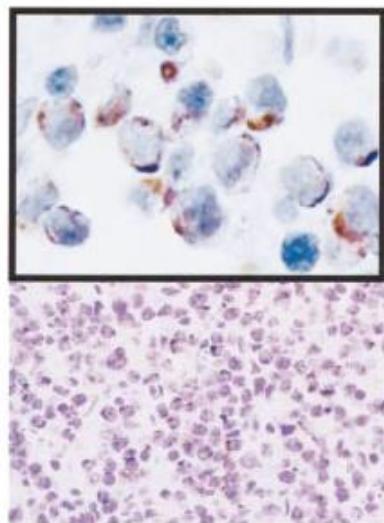
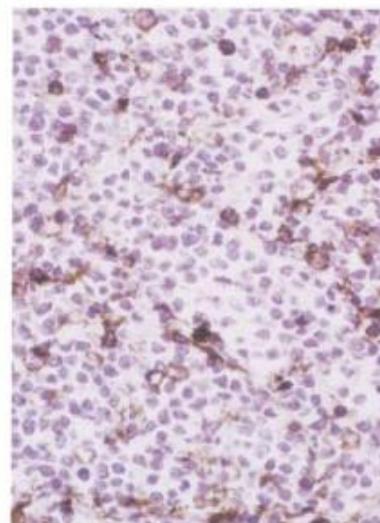


Figure 1. Computed tomography of a large right suprarenal mass involving the liver.

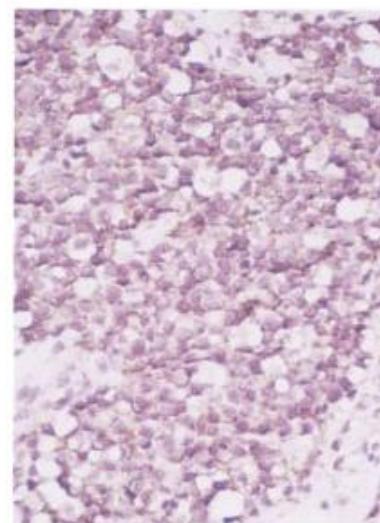
CD45 - Leucocyte common antigen (LCA)



A



B



C

Figure 3. Note immunoreactivity of the lymphoma cells for cytokeratin (A) and CD20 (C) but not CD45 (B) (original magnification $\times 100$, inset $\times 250$)

Molecular Biologic Findings

Monoclonal rearrangement of the immunoglobulin heavy chain gene was identified by polymerase chain reaction (data not shown).

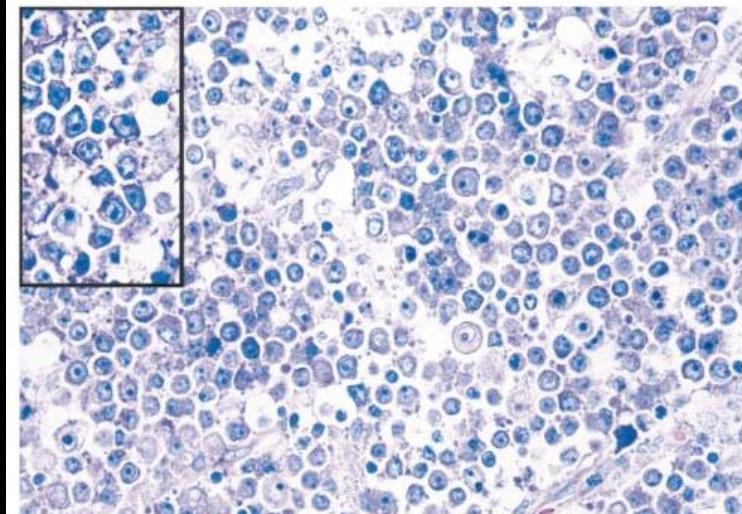


Figure 2. Light microscopic appearance of the tumor (Giemsa stain, original magnification $\times 100$, inset $\times 250$).

CD45 - Leucocyte common antigen (LCA)

MATERIALS AND METHODS

We performed immunohistochemical stains for cytokeratin (AE1/AE3. Cell Marque. Austin. Tex: CAM5.2. Becton Dickinson. San Jose, Calif; cytokeratins 5/6, Zymed, San Francisco, Calif; cytokeratin 7, Dako Corporation, Carpinteria, Calif; cytokeratin 20, Dako; 34 β E12, Enzo, New York, NY), CD3, CD20, CD30, CD45RO, CD68, κ light chain, λ light chain, myeloperoxidase, epithelial membrane antigen, neuron-specific enolase, synaptophysin, S100 protein, HMB-45 (Dako), and chromogranin A (Cell Marque) on a TechMate 500 with a ChemMate Secondary Detection Kit–Peroxidase/DAB (Ventana Medical Systems, Tucson, Ariz). The histologic sections were pretreated by steaming in citrate buffer solution (Target Retrieval Solution, Dako) for 30 minutes at 99°C.

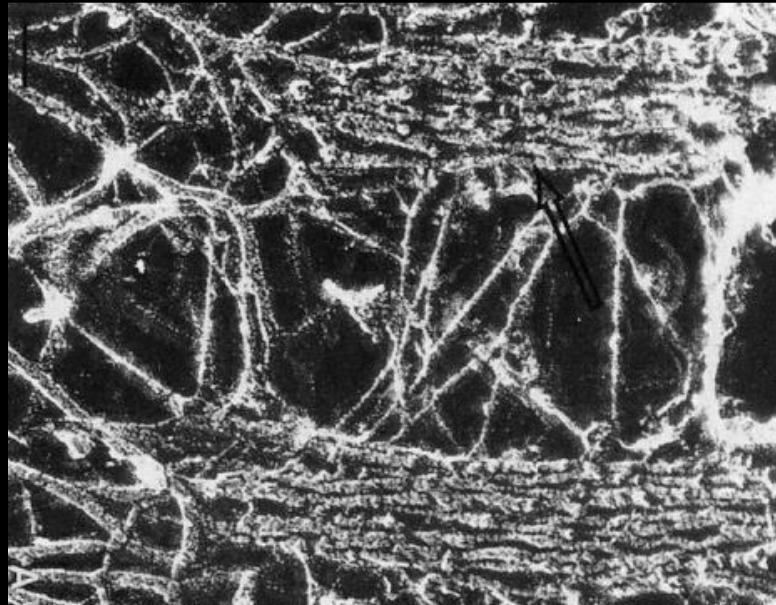
The monoclonal antibodies AE1/AE3 (working concentration, 0.4 μ g of protein/mL) were applied for 25 minutes at room temperature. The immunostaining was repeated twice, each time with identical results.

Primary panel for the unknown primary tumour

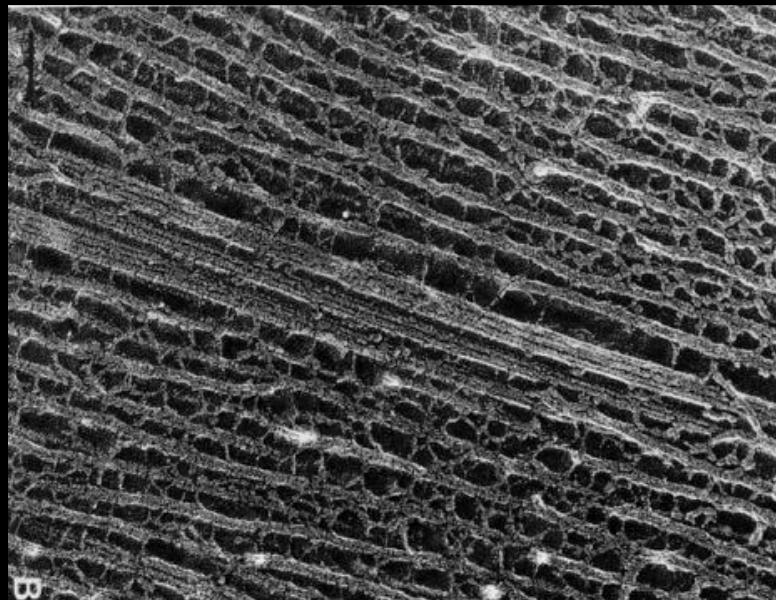
	CD45	Pan-CK	S-100	VIM
Haemato-lymphoid neoplasms	+/-(-)	-/(+)	-/(+)	+/-(-)
Epithelial neoplasms	-	+/-(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cellular filaments

Microfilaments: (6 nm)



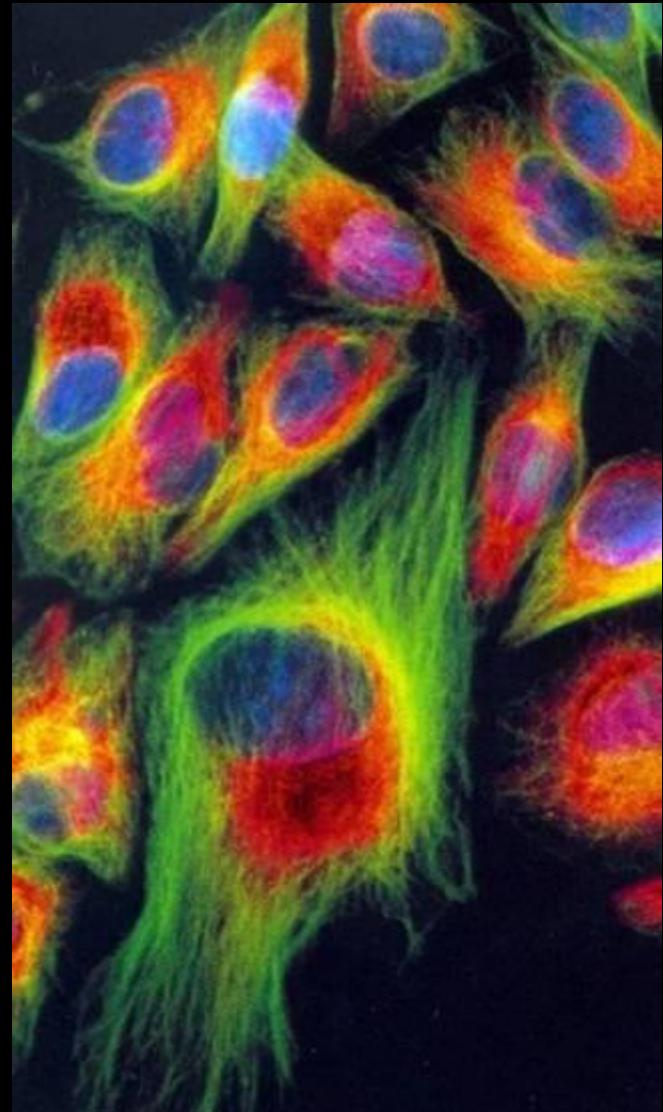
Intermediate filaments
(7- 11 nm)



Microtubuli (23 nm)

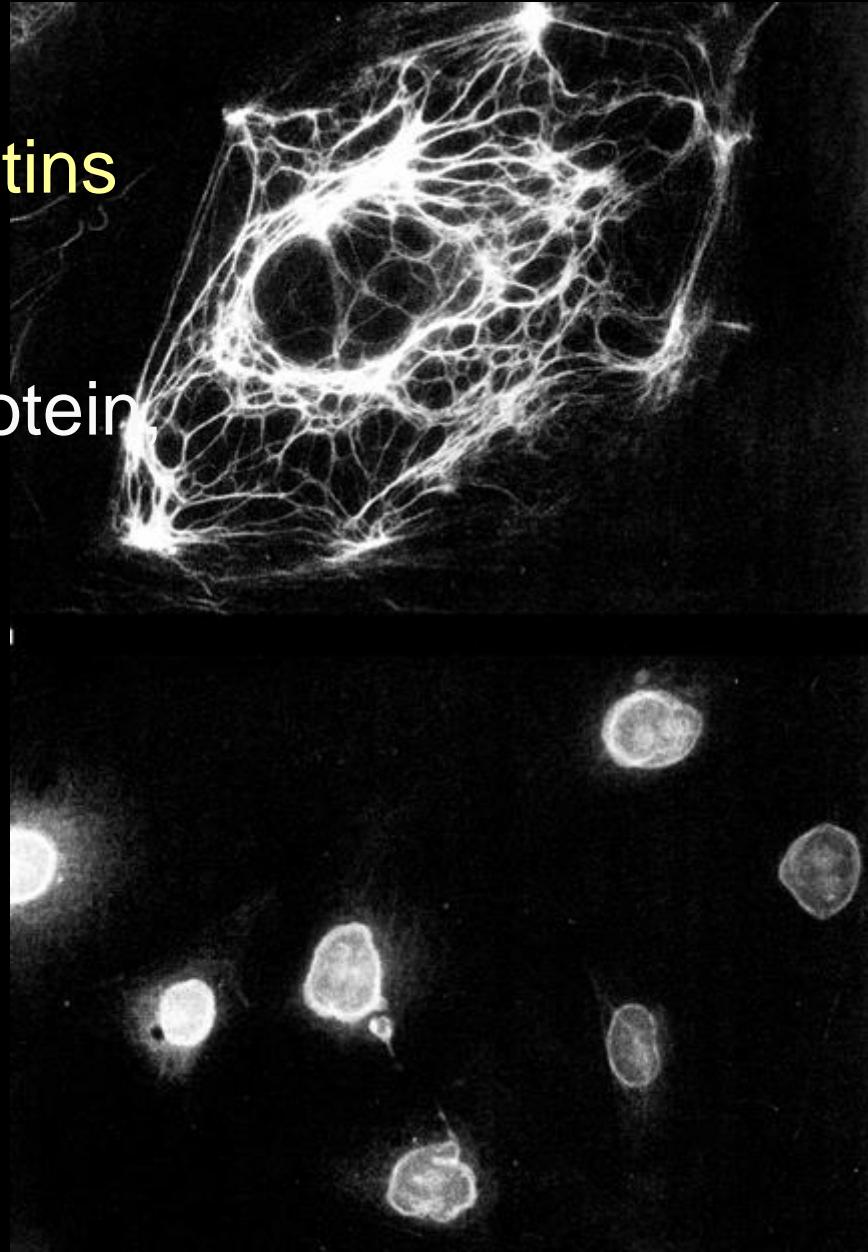
Intermediate filaments

- Group of mainly cytoplasmic filaments 7 – 11 nm in diameter
- Part of the cytoskeleton in virtually all cells, creating a meshwork and connecting nuclear membrane with cell membrane
- Often associated with microfilaments (6 nm) and microtubules (23 nm)
- Important for mechanical strength and cellular functions



Intermediate filaments - 5 classes

- I acidic cytokeratins
- II basic-neutral cytokeratins
- III vimentin, desmin,
glial fibrillary acidic protein,
peripherin
- IV neurofilament protein,
 α -internexin, nestin
- V lamins



Cytokeratins as tonofilaments



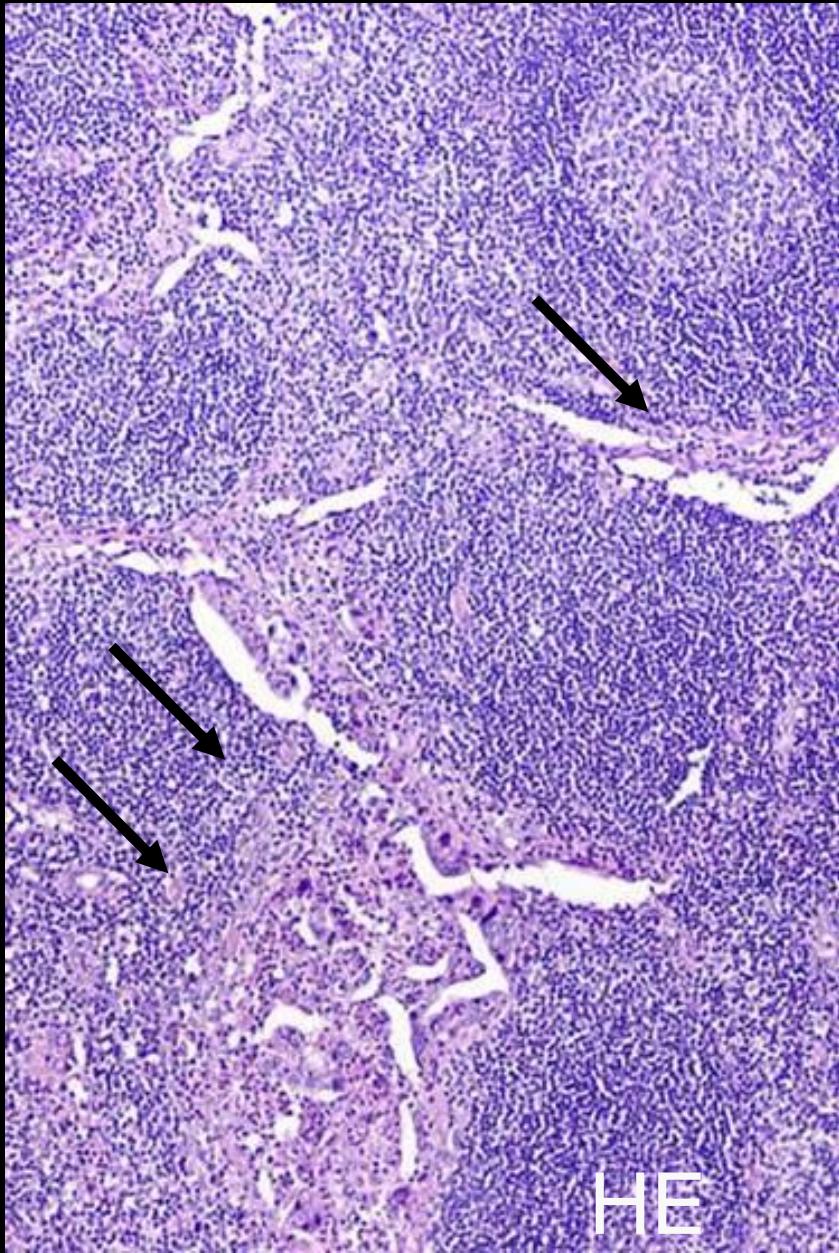
Cytokeratin intermediate
filaments attached
to desmosomes

Drochmans et al.
J Cell Biol. 1978, 79:427

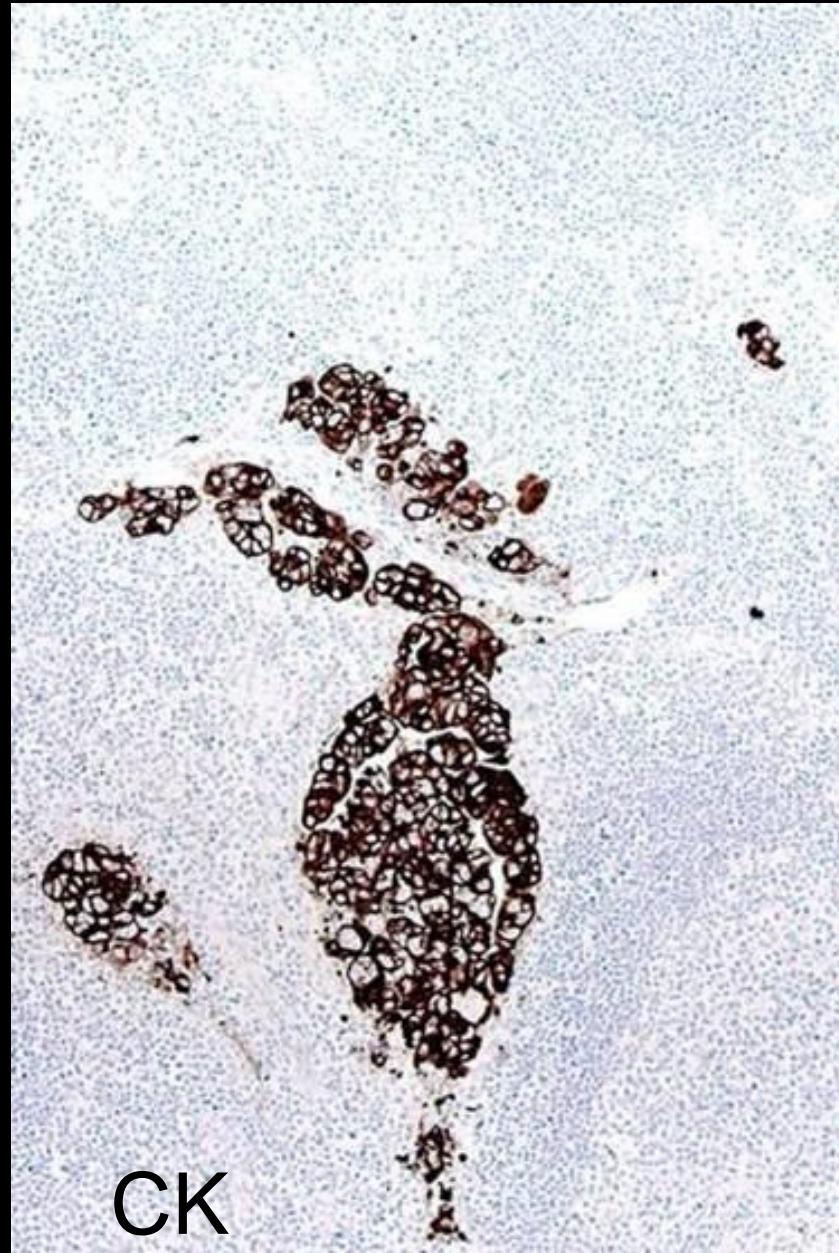
Cytokeratins in diagnostic pathology

- Cytokeratins (CKs) belong to the most fundamental markers of epithelial differentiation
- CKs comprise a large family of subtypes. Different cell types express different patterns of CK subtypes
- Cancers generally express CK patterns that at least in part represent the pattern of the putative cell of origin
- Metastases express CK patterns fairly concordant with those of the primary tumours

Micrometastases identified by cytokeratin



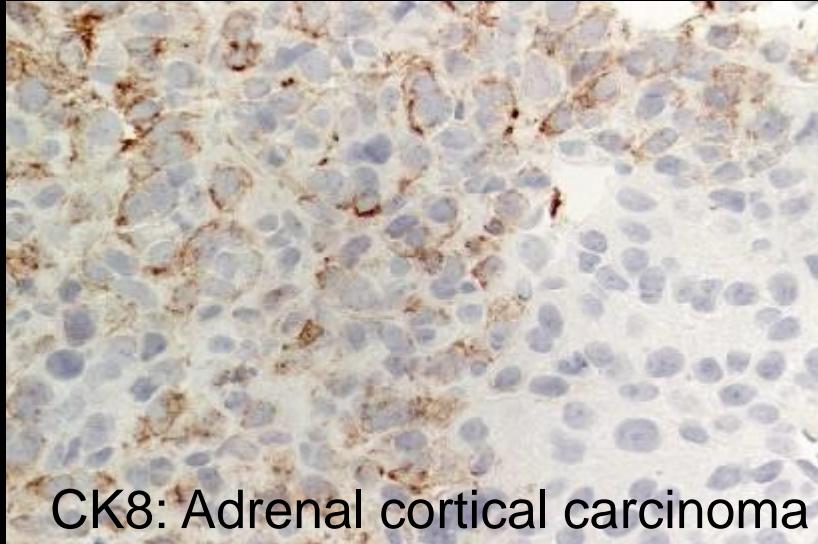
HE



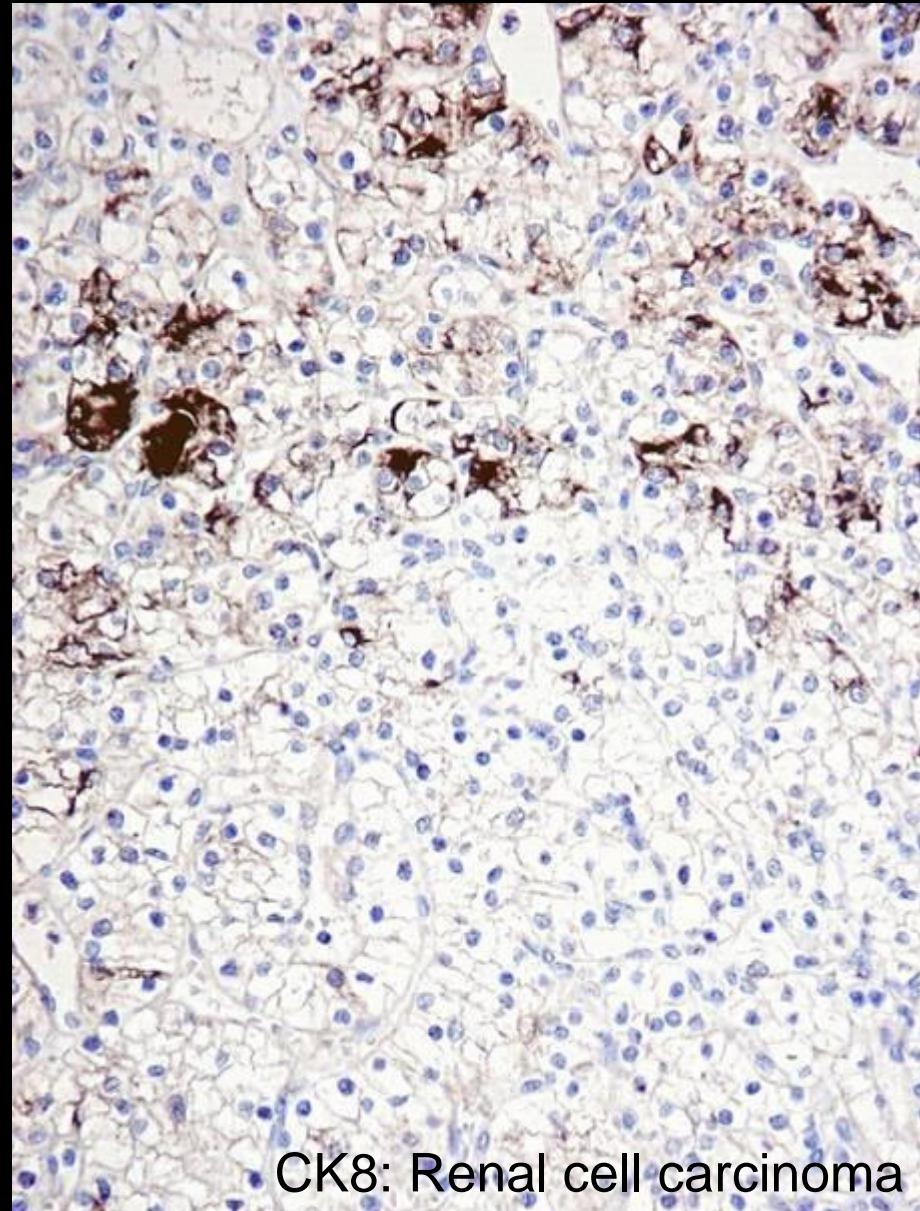
CK

Low molecular weight cytokeratins in carcinomas

- Carcinomas “always” LMW-CK-positive, except some cases of
 - Renal cell carcinoma
 - Adrenal cortical carcinoma
 - Small cell carcinoma



CK8: Adrenal cortical carcinoma

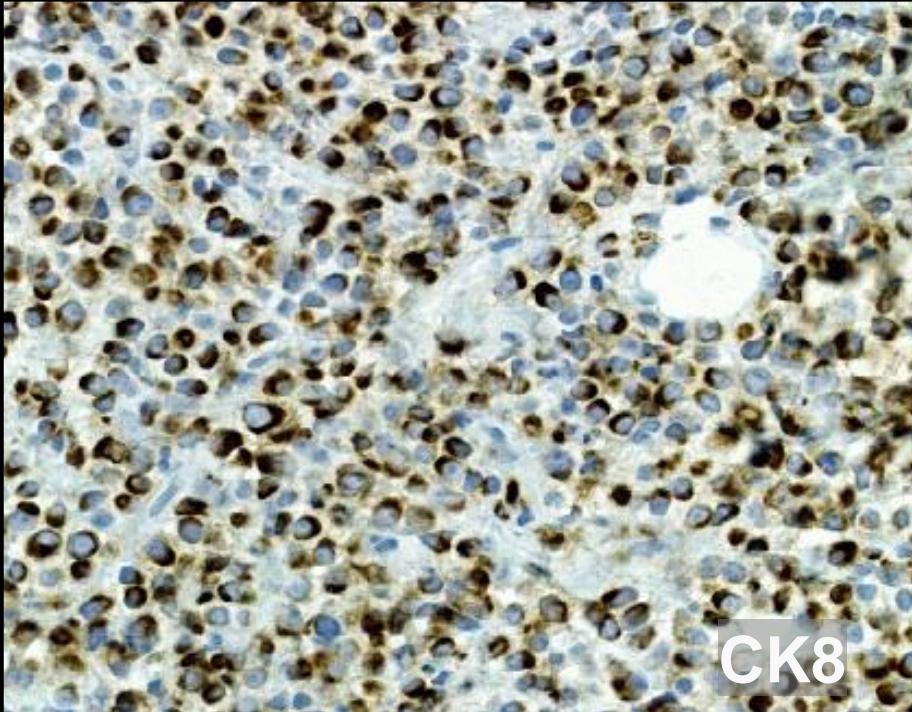


CK8: Renal cell carcinoma

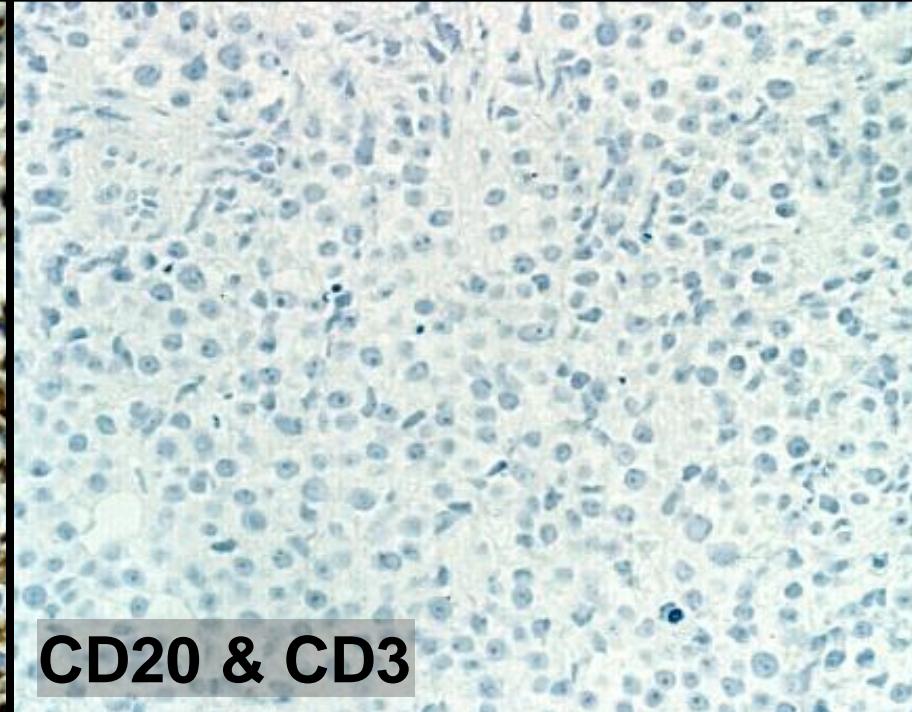
Primary panel for the unknown primary tumour

	CD45	Pan-CK	S-100	VIM
Haemato-lymphoid neoplasms	+/-(-)	-/(+)	-/(+)	+/-(-)
Epithelial neoplasms	-	+/-(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cytokeratins in non-epithelial tumours



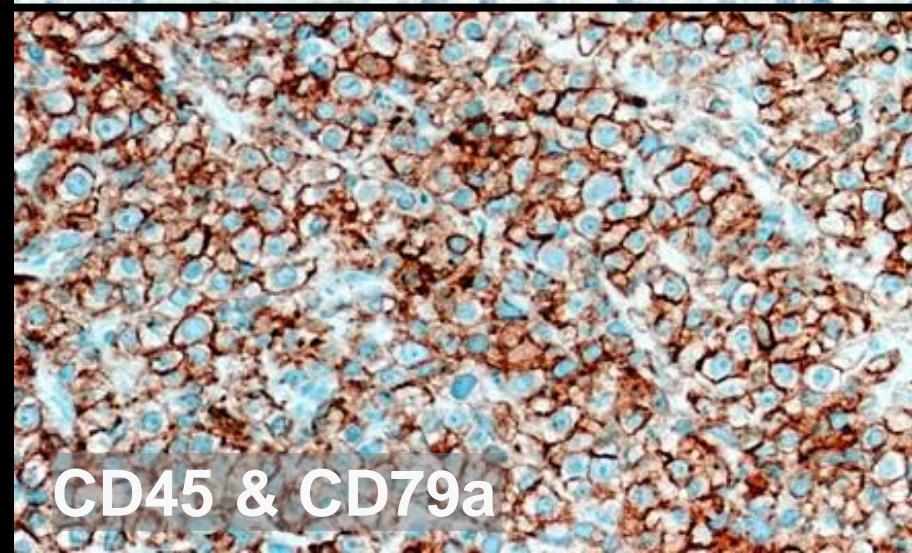
CK8



CD20 & CD3

♀ 42 y, tumour infiltrating
retroperitoneum

Malignant lymphoma !

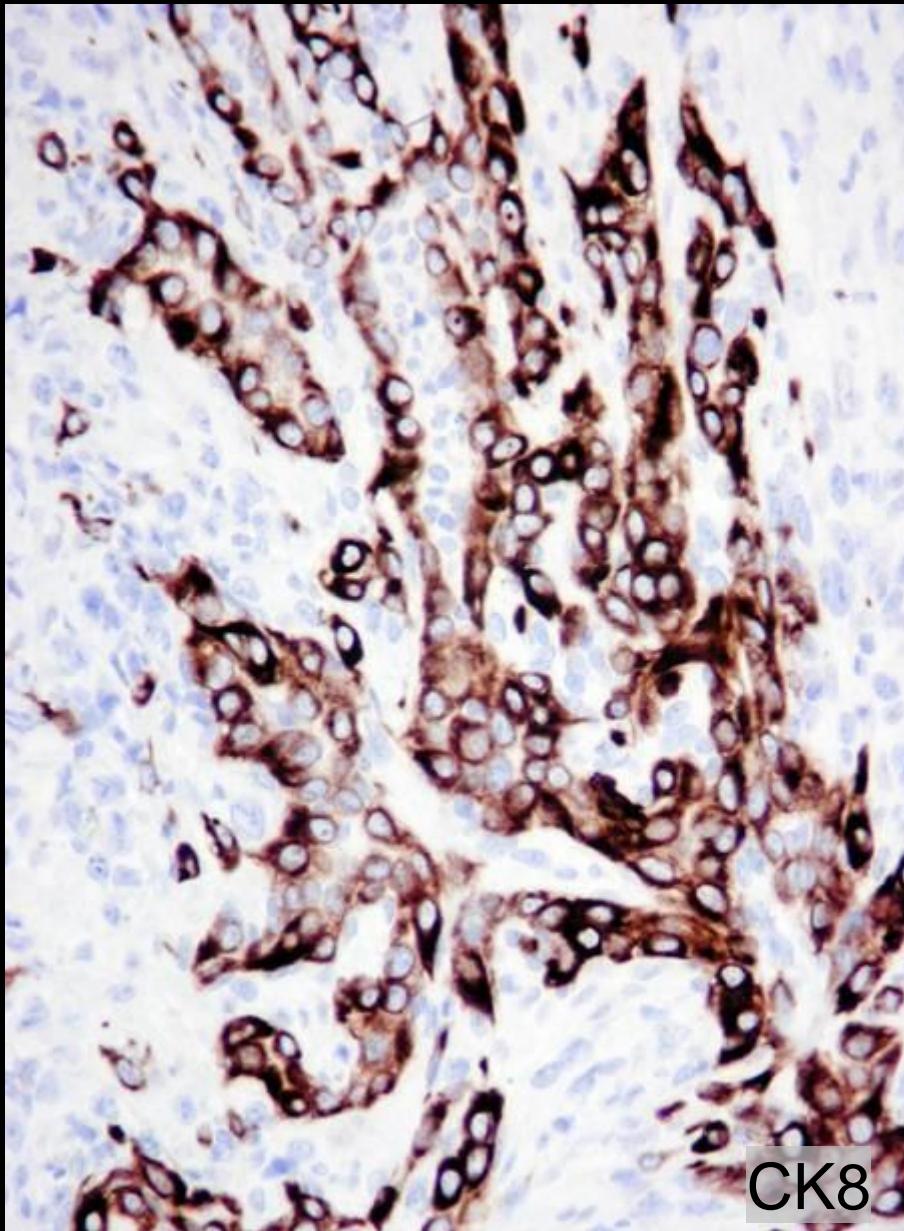


CD45 & CD79a

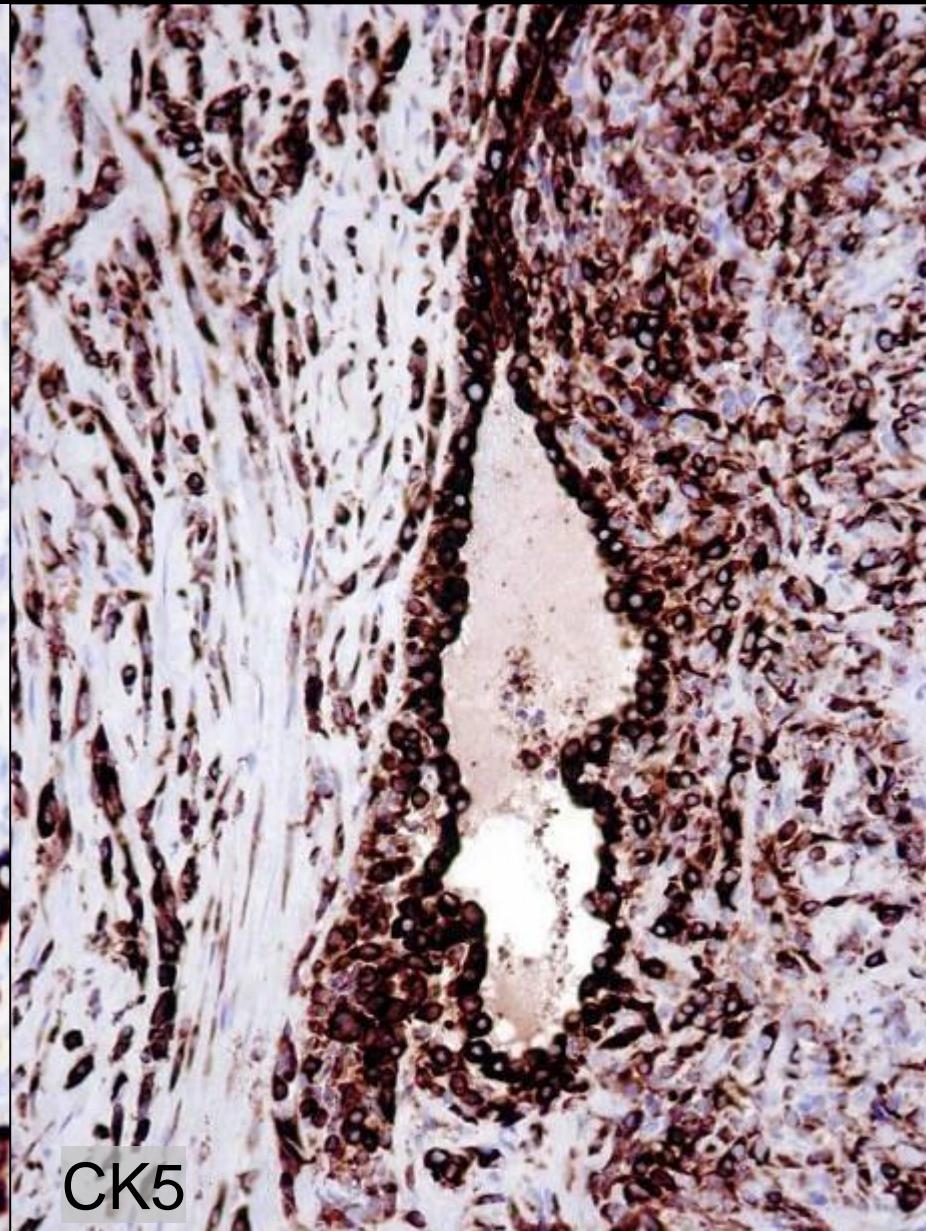
Primary panel for the unknown primary tumour

	CD45	Pan-CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cytokeratins in malignant mesothelioma



CK8

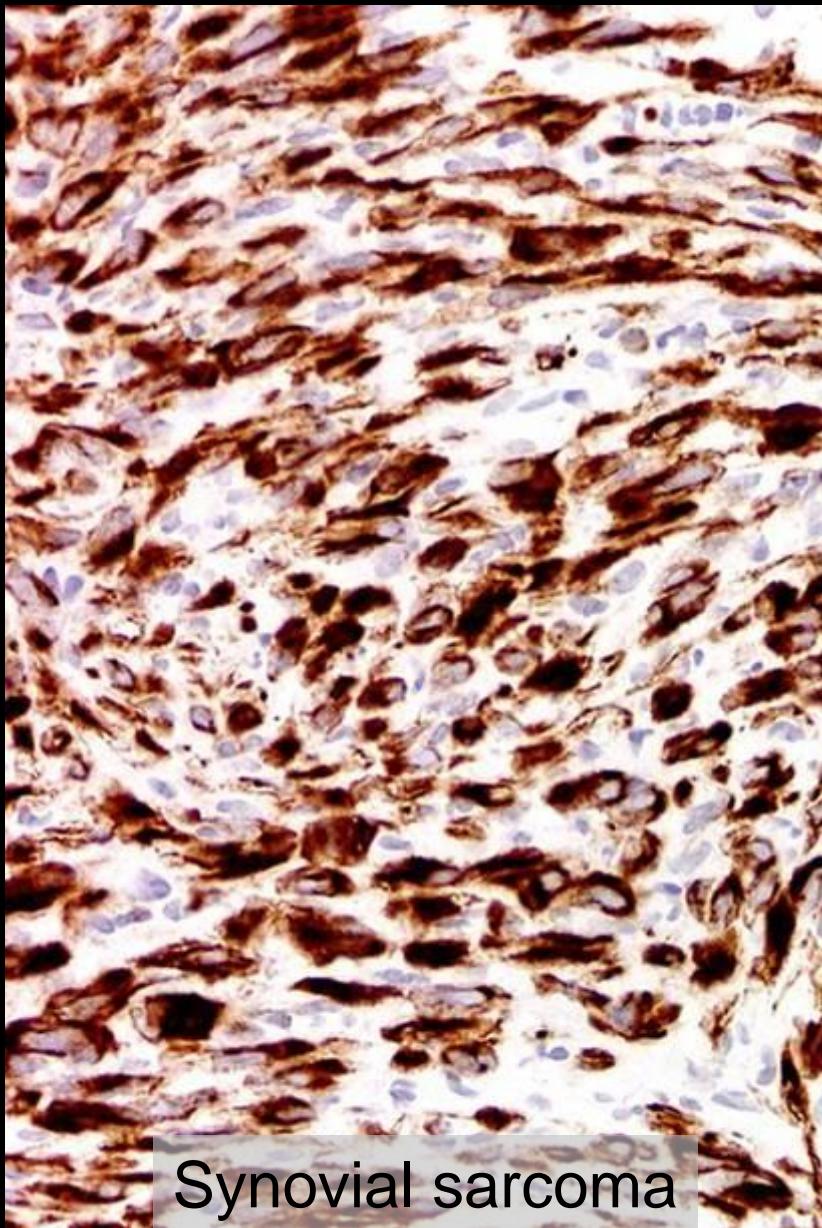


CK5

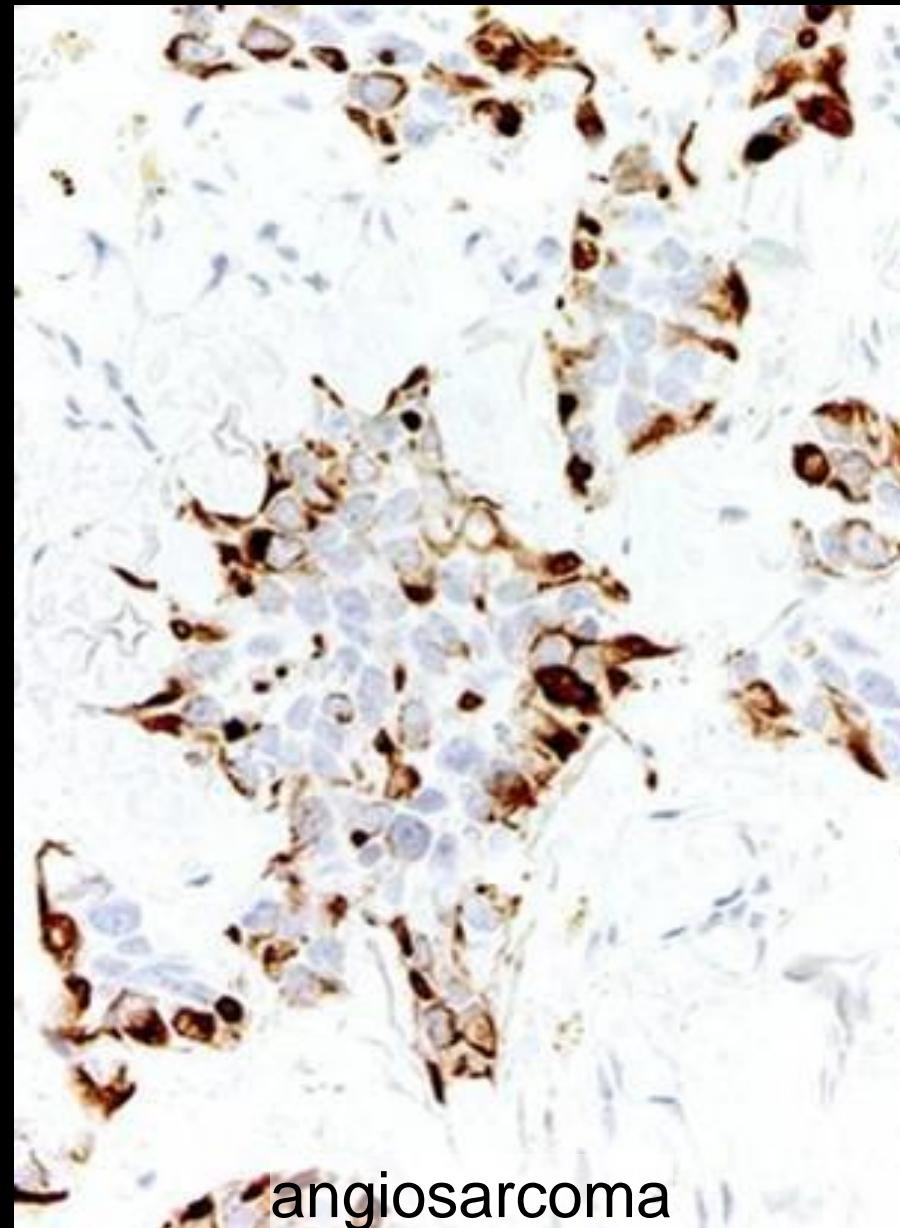
Primary panel for the unknown primary tumour

	CD45	Pan-CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/-
Epithelial neoplasms	-	+/(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cytokeratins in sarcomas

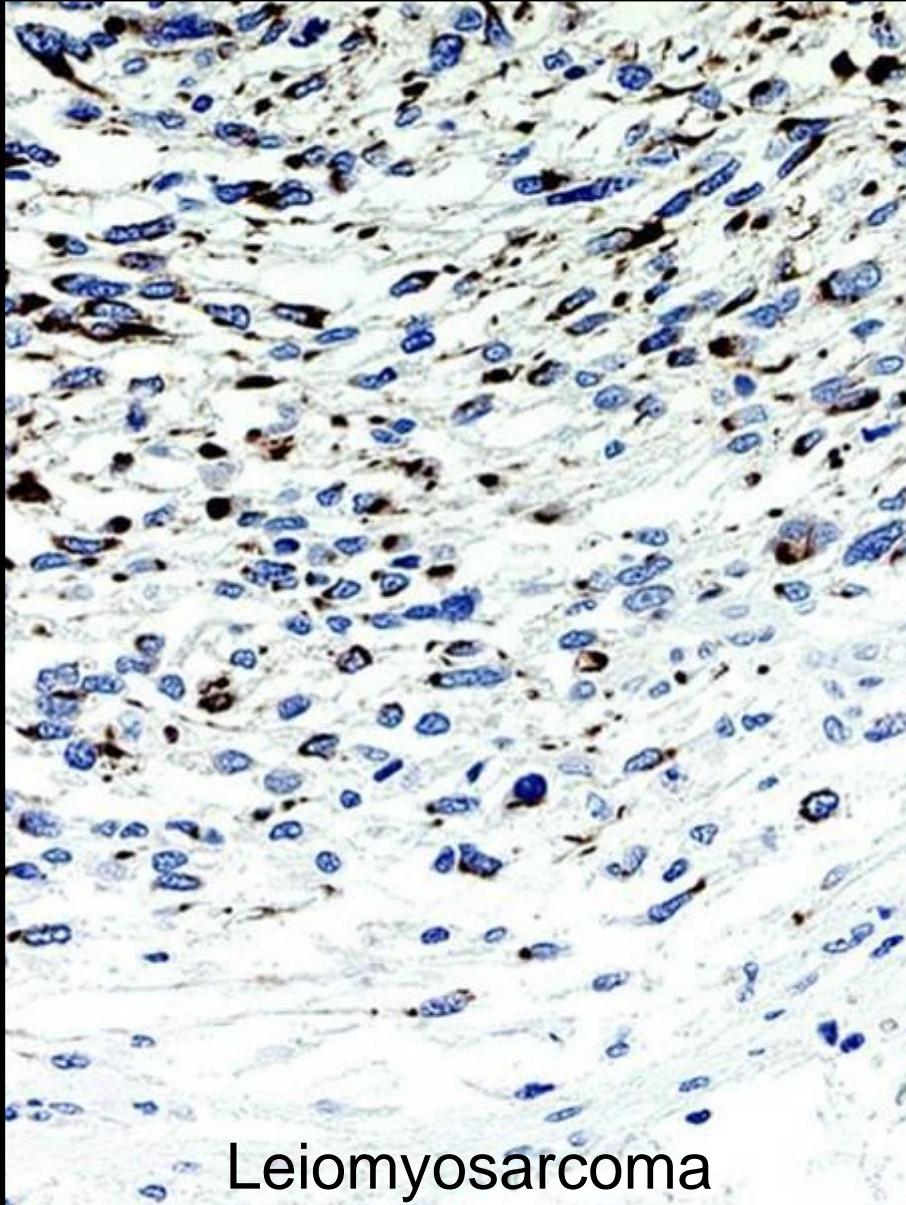


Synovial sarcoma

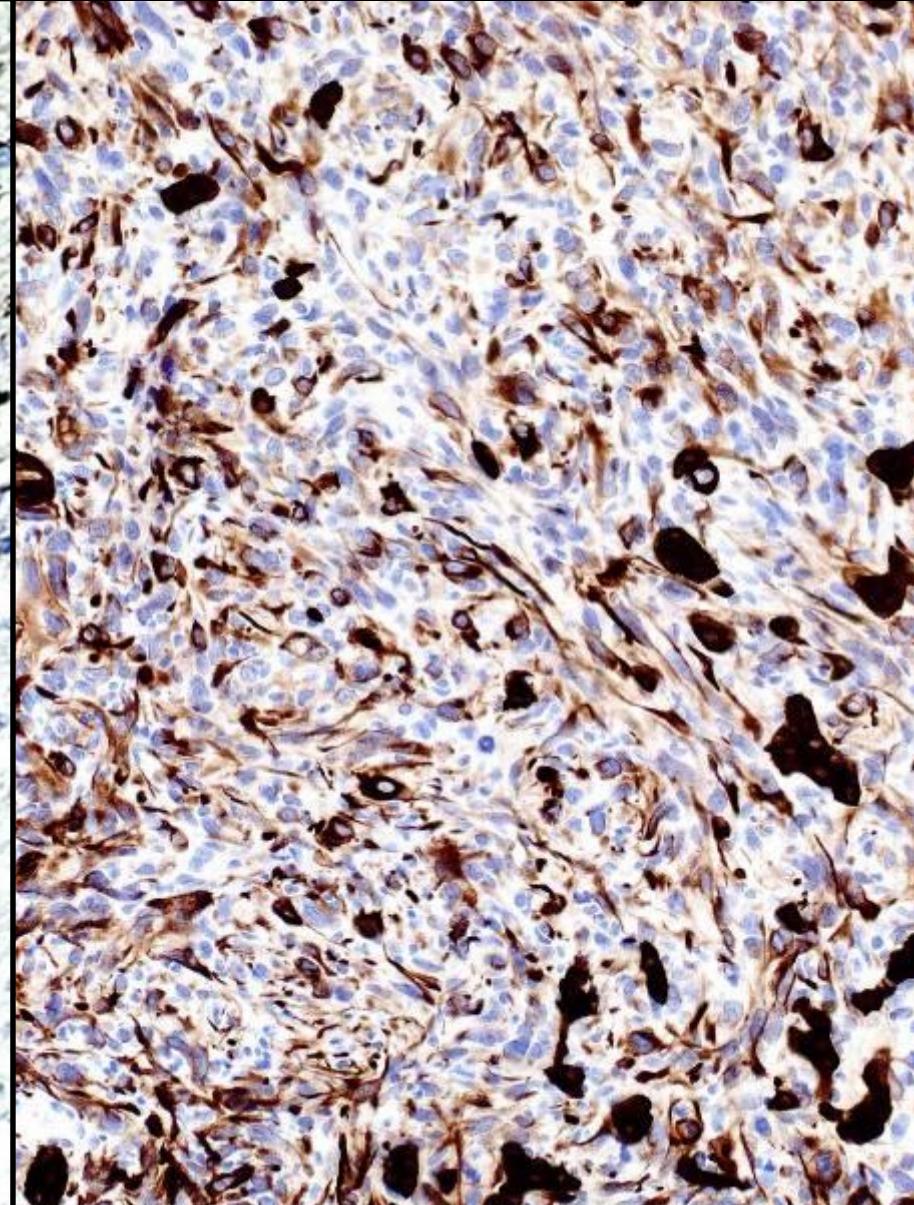


angiosarcoma

Cytokeratins in non-epithelial tumours



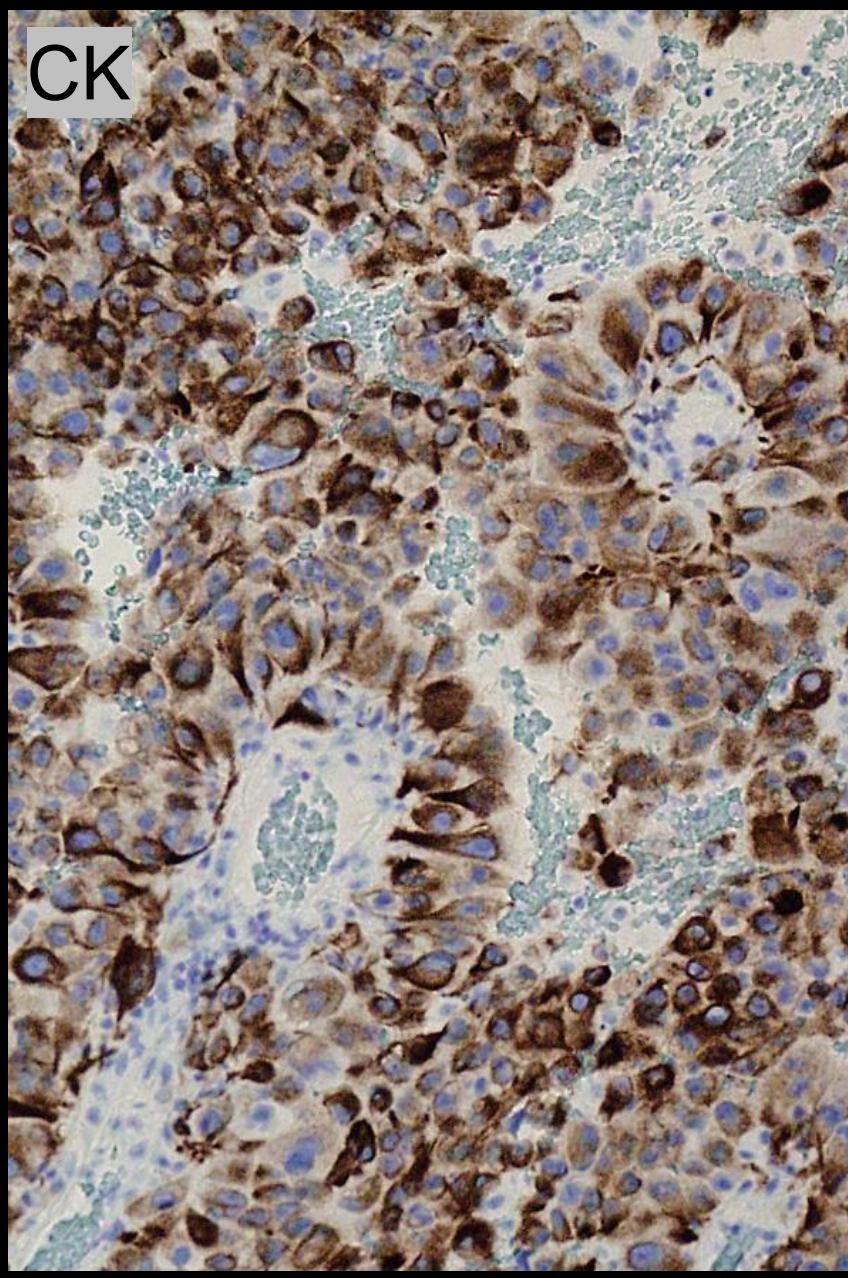
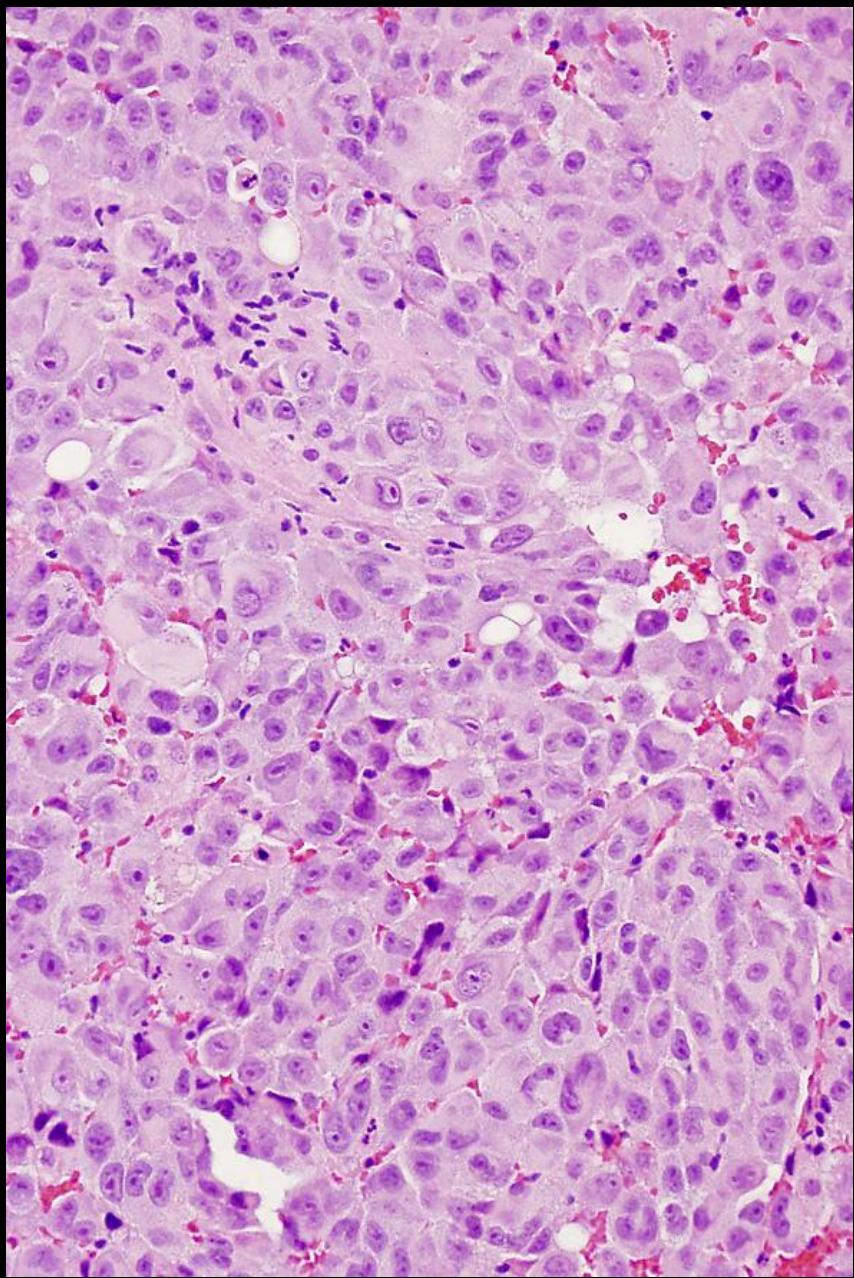
Leiomyosarcoma



Primary panel for the unknown primary tumour

	CD45	Pan-CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/-	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

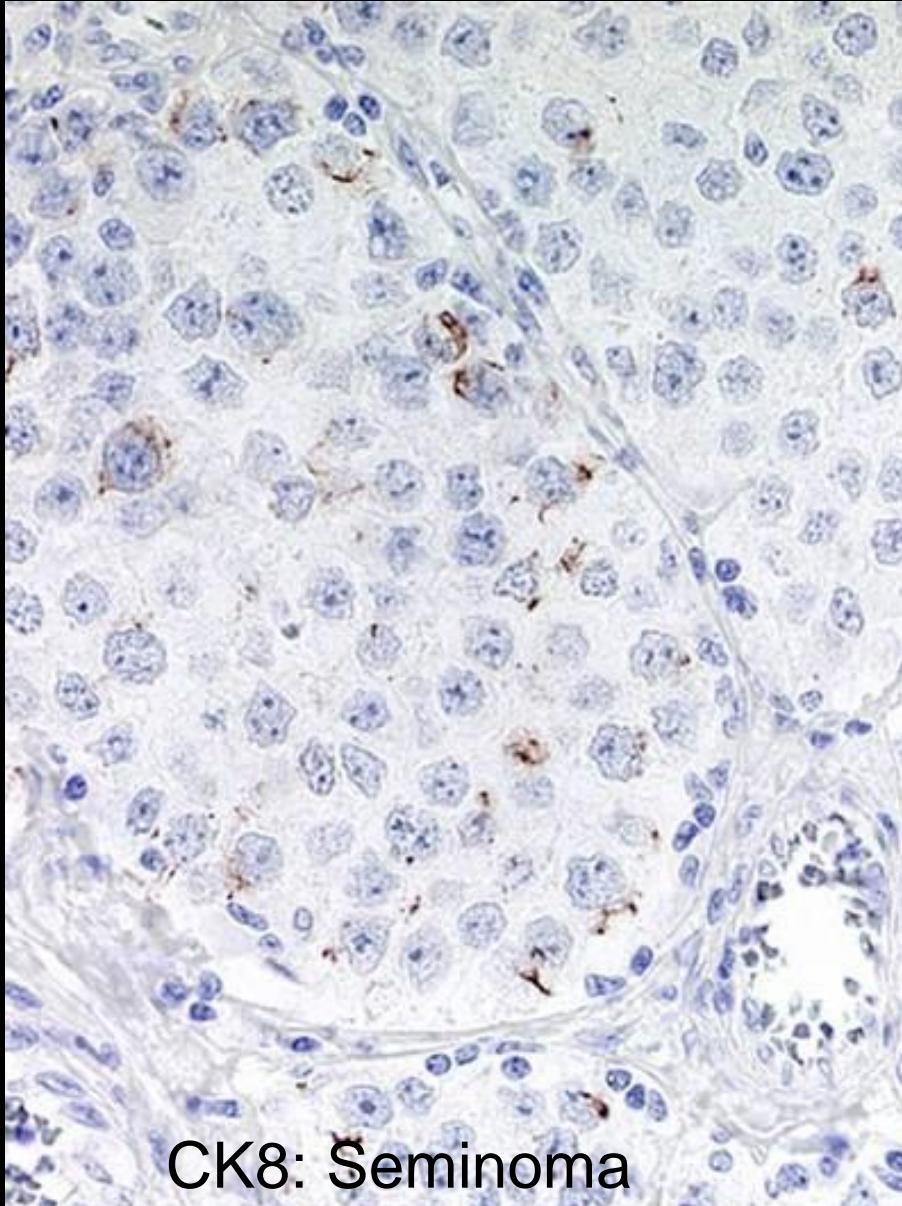
Cytokeratins in malignant melanoma



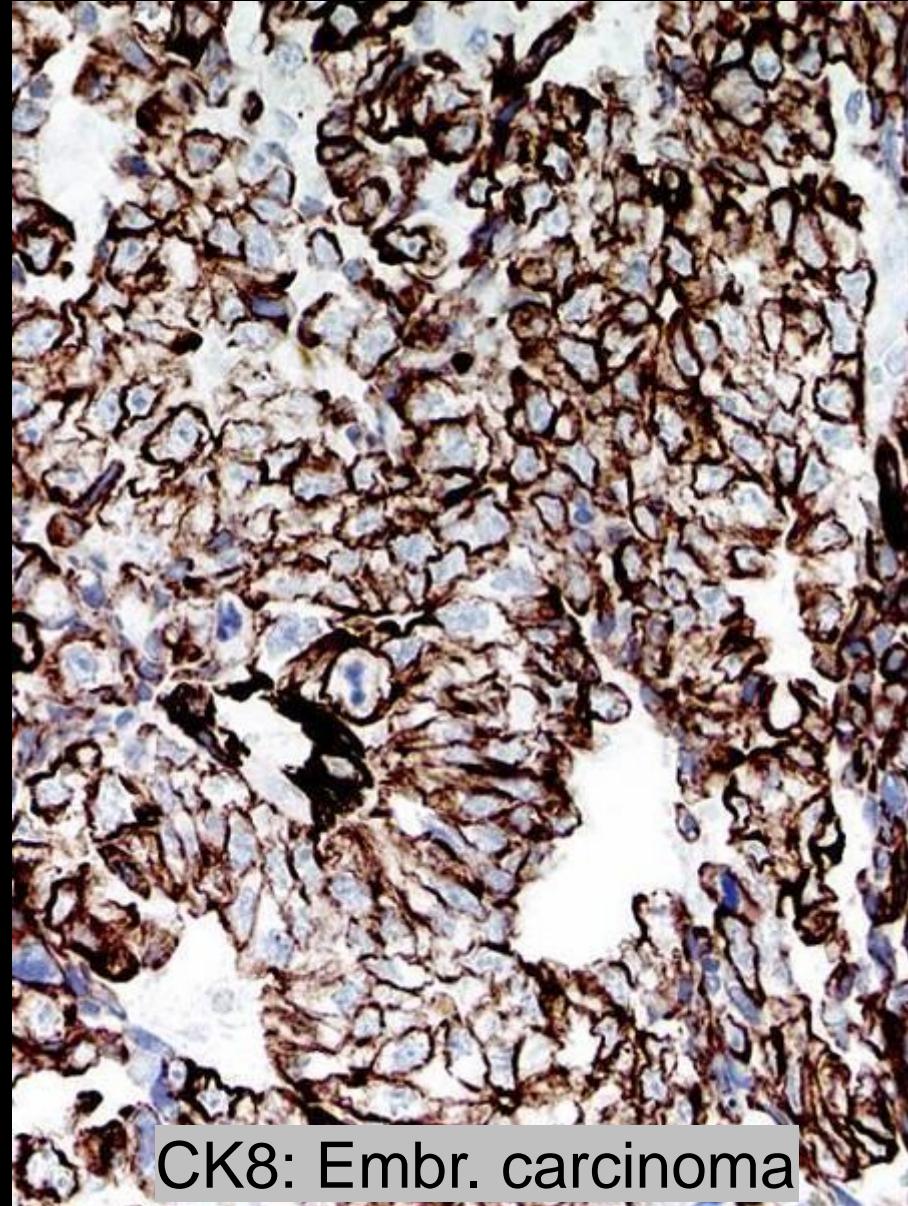
Primary panel for the unknown primary tumour

	CD45	Pan-CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/-	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Cytokeratins in germ cell tumours



CK8: Seminoma



CK8: Embr. carcinoma

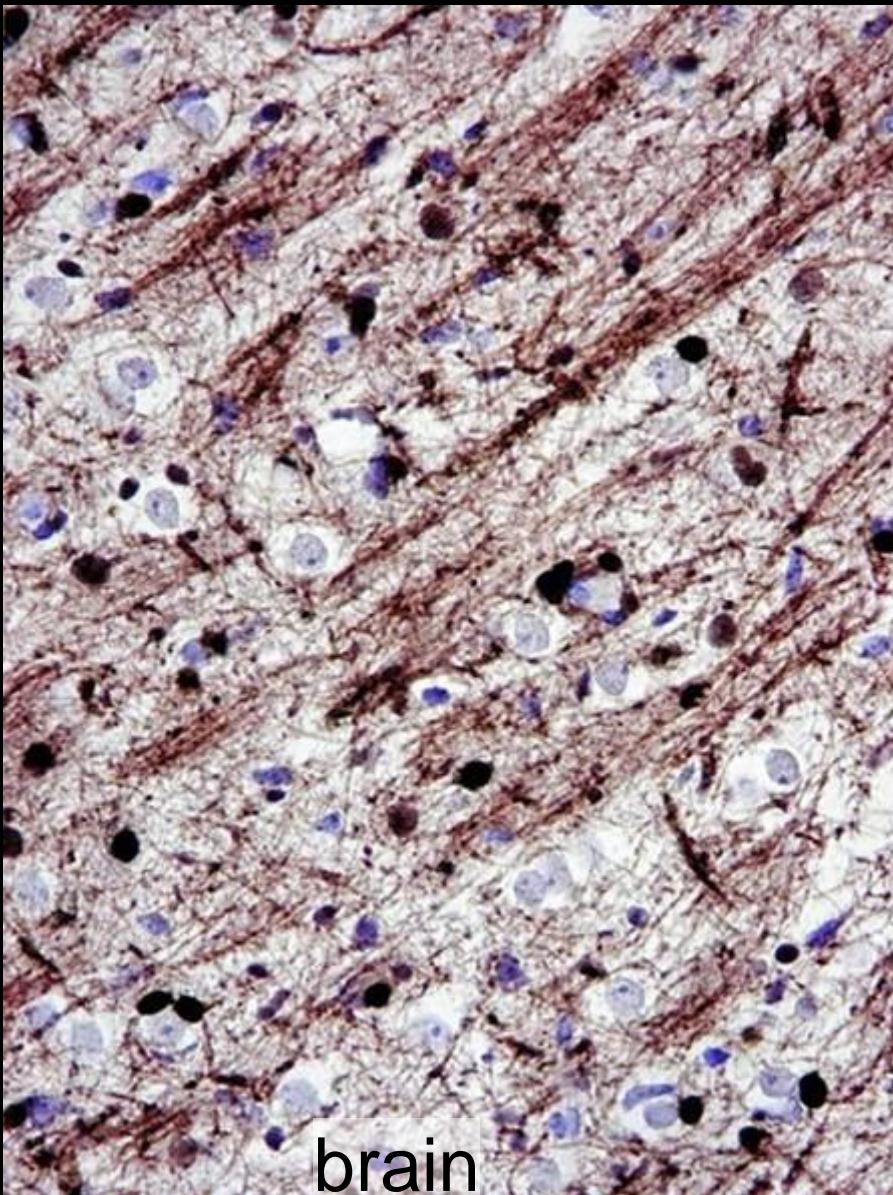
Primary panel for the unknown primary tumour

	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/(-)	-/(+)	-/(+)	+/(-)
Epithelial neoplasms	-	+/-	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

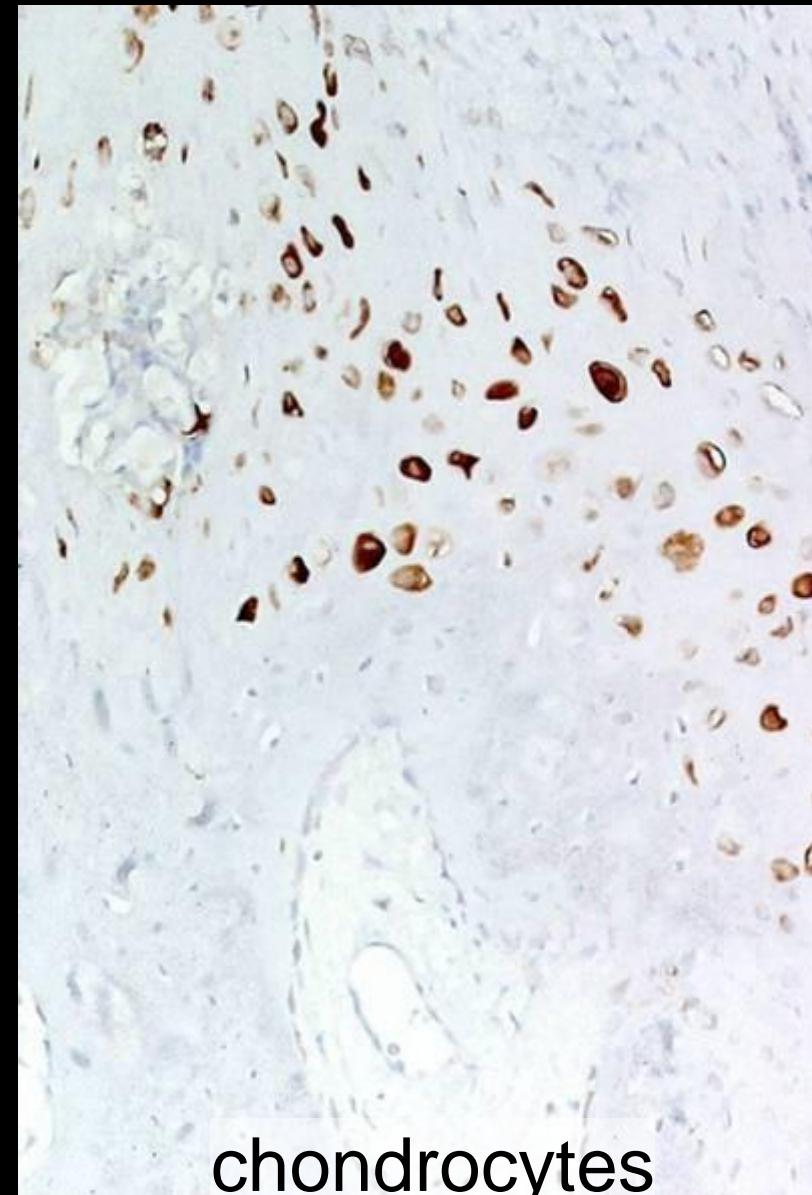
S-100 protein

- Family of acid calcium binding proteins 9/13 kDa
- Located in nuclei, cytoplasm and cell membranes
- at least 10 α -chains and one β -chain creating homo- and heterodimers
- S-100 β -chain mainly found in
 - Melanocytes
 - Glial cells
 - Langerhans' cells / interdigitating reticulum cells
 - Fat cells
 - Myoepithelial cells
- Polyclonal antibodies primarily detects the β -chain

S-100 protein

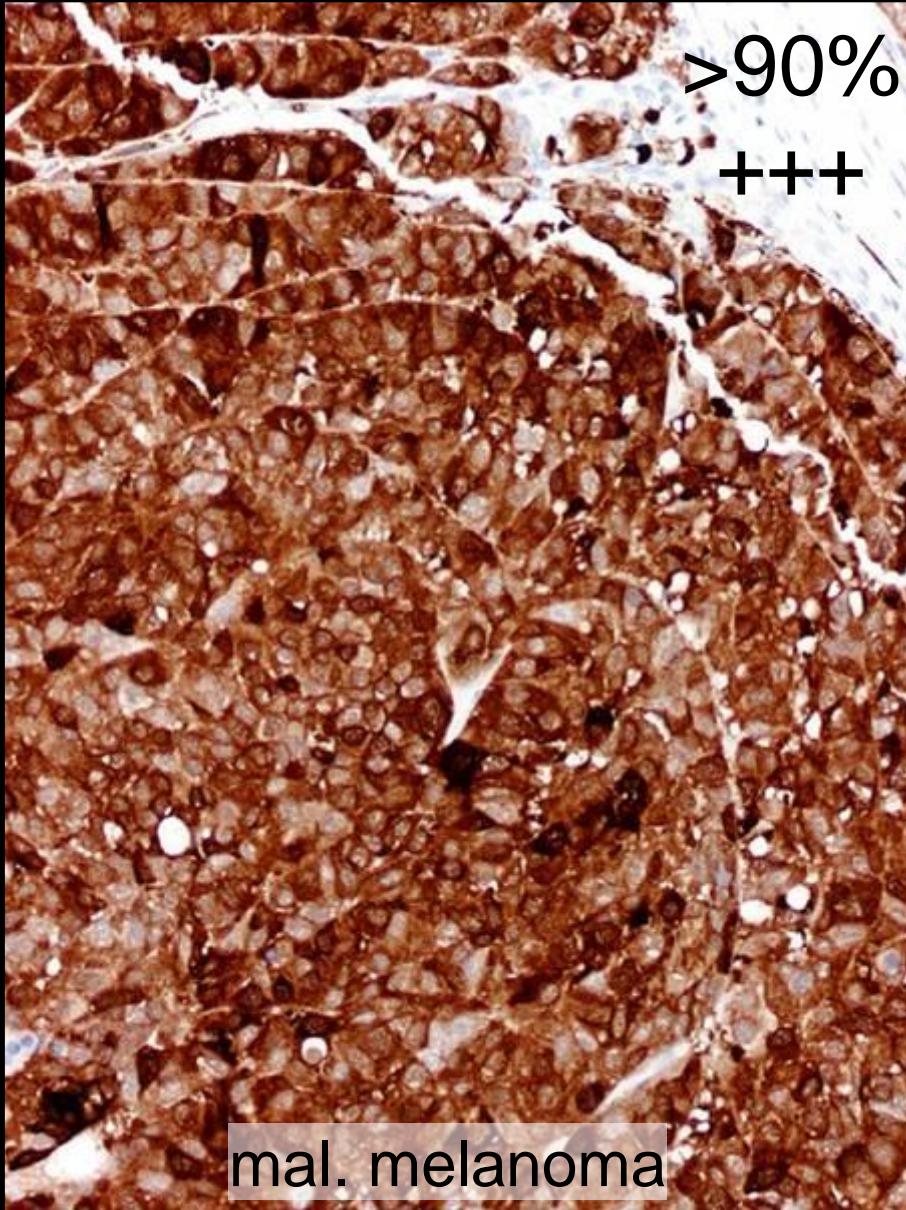


brain

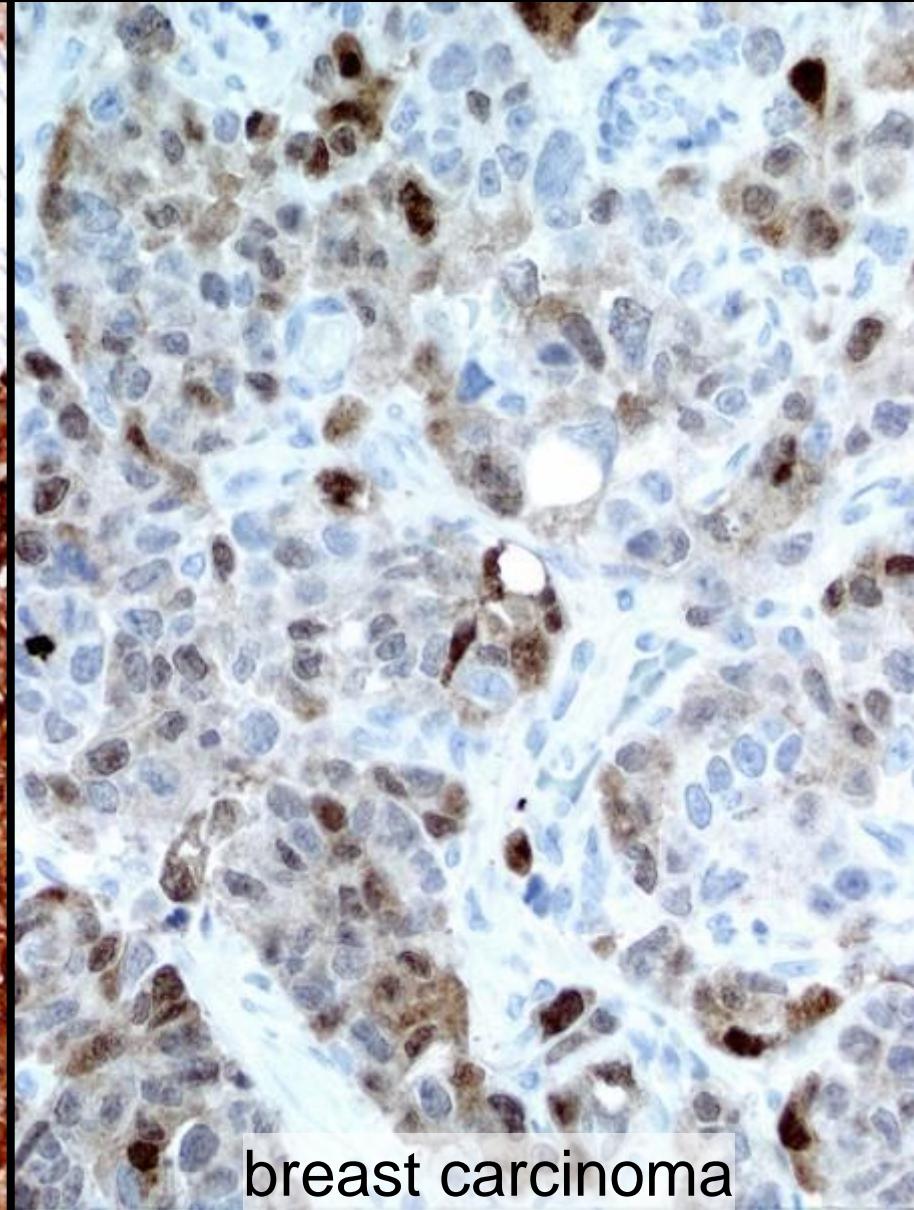


chondrocytes

S-100 in malignant tumours



mal. melanoma



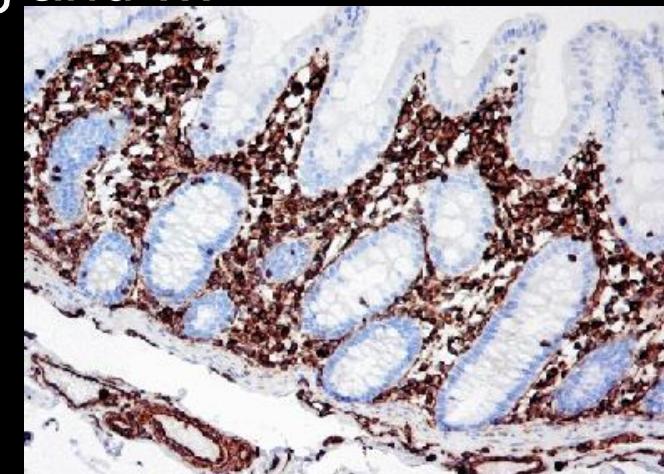
breast carcinoma

Primary panel for the unknown primary tumour

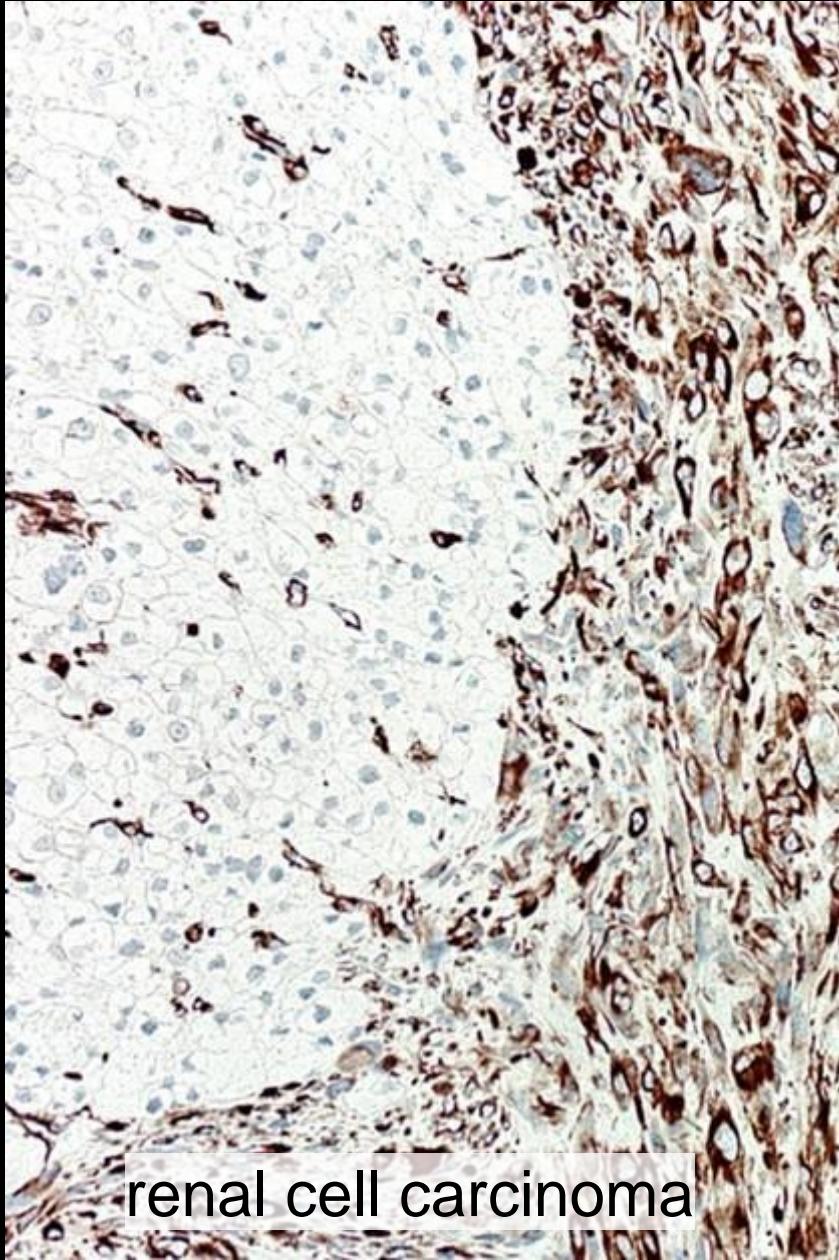
"Real"	CD45	CK	S-100	VIM
Haemato-lymphoid neoplasms	+/-(-)	-/(+)	-/(+)	+/-(-)
Epithelial neoplasms	-	+/-(-)	-/+	-/+
Mesothelial neoplasms	-	+	-	+
Mesenchymal and neuronal neoplasms	-	-/(+)	-/+	+
Non-neuronal neuroepithelial neoplasms	-	-/(+)	+	+
Germ cell neoplasms	-	-/+	-/+	+

Vimentin

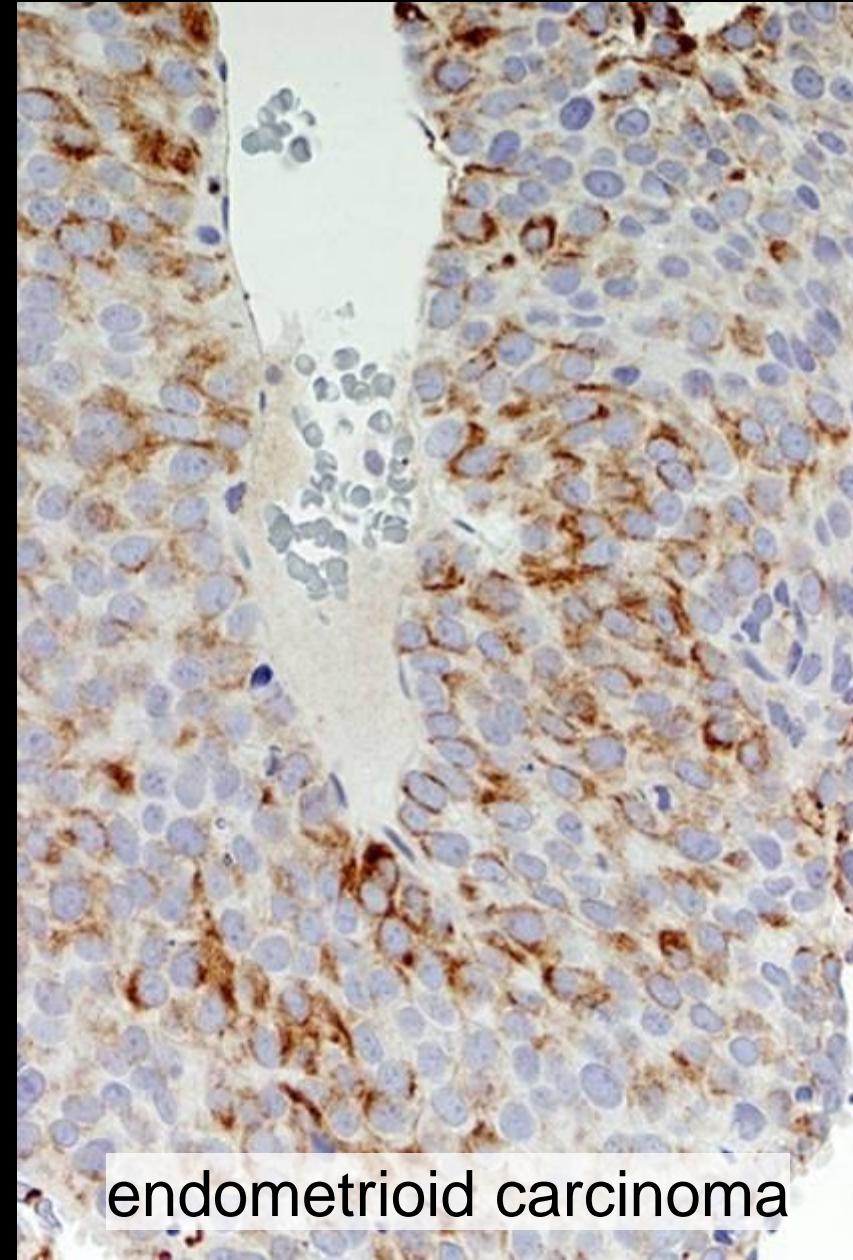
- Cytoplasmic intermediate filament, 57 kDa
- Present in all mesenchymal cells
- Present in early stages of all cells, replaced by other intermediate filaments in most non-mesenchymal cells
- Coexpressed with cytokeratin in some epithelia
 - Endometrium, renal tubules, thyroid gland ...
- Coexpressed with cytokeratin in some non-epithelial cells
 - Mesothelium



Vimentin in carcinomas

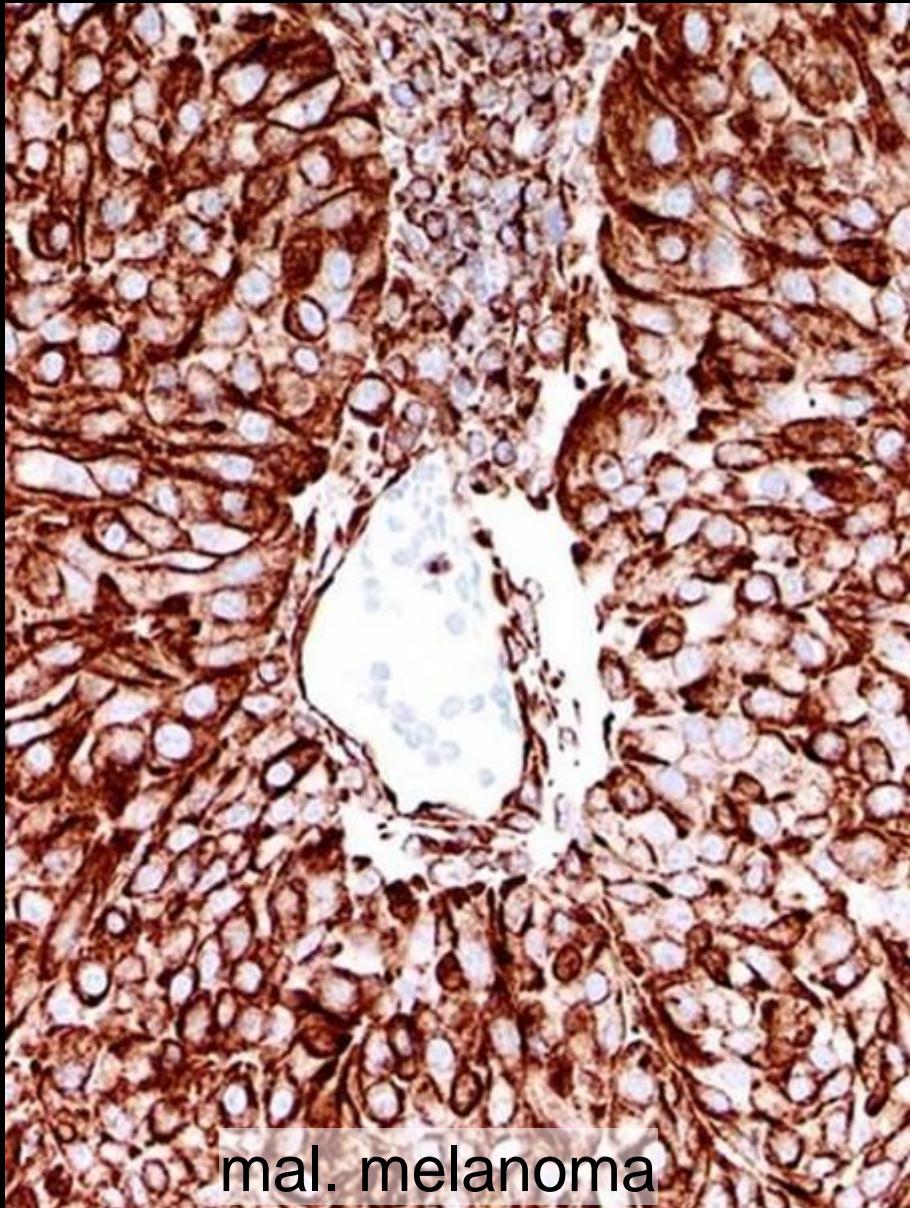


renal cell carcinoma

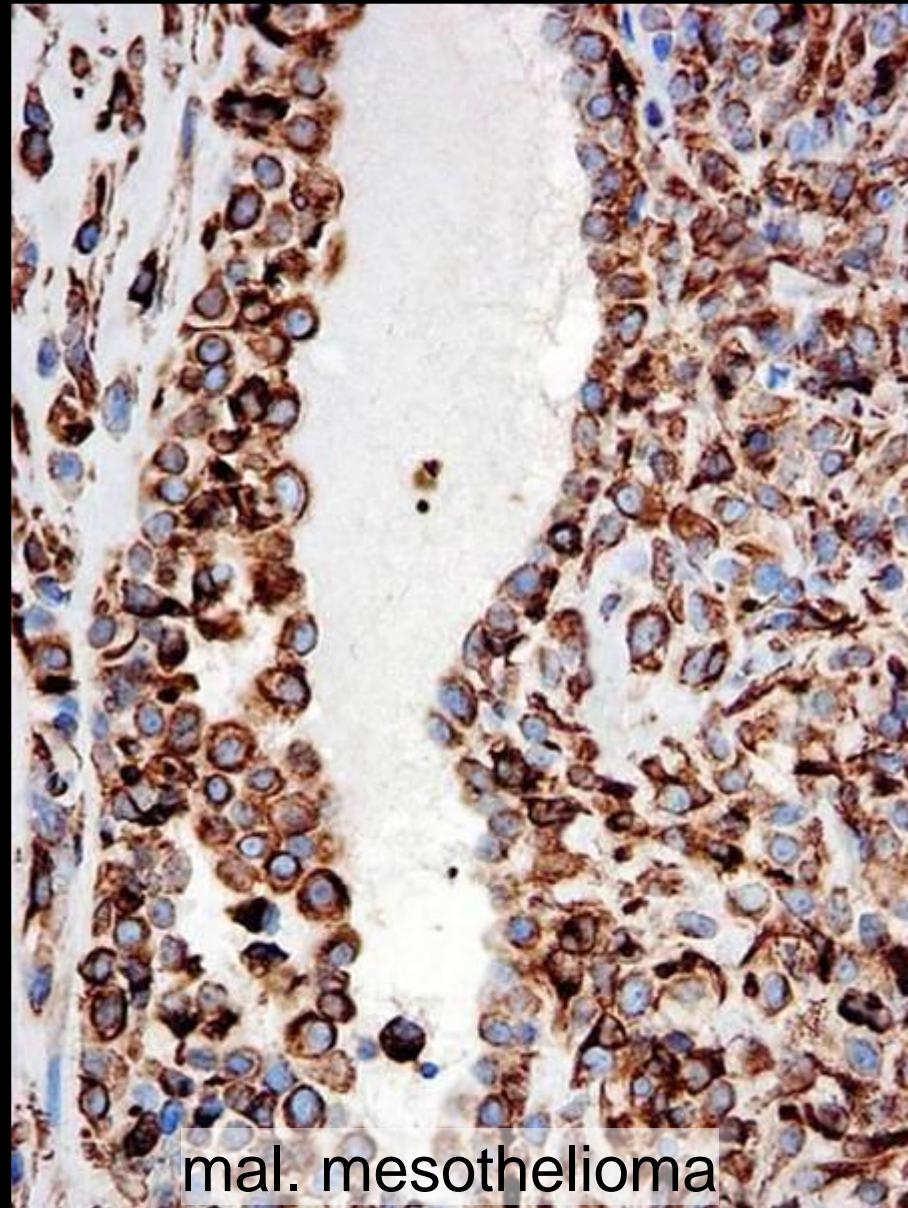


endometrioid carcinoma

Vimentin in non-epithelial tumours



mal. melanoma



mal. mesothelioma

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

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

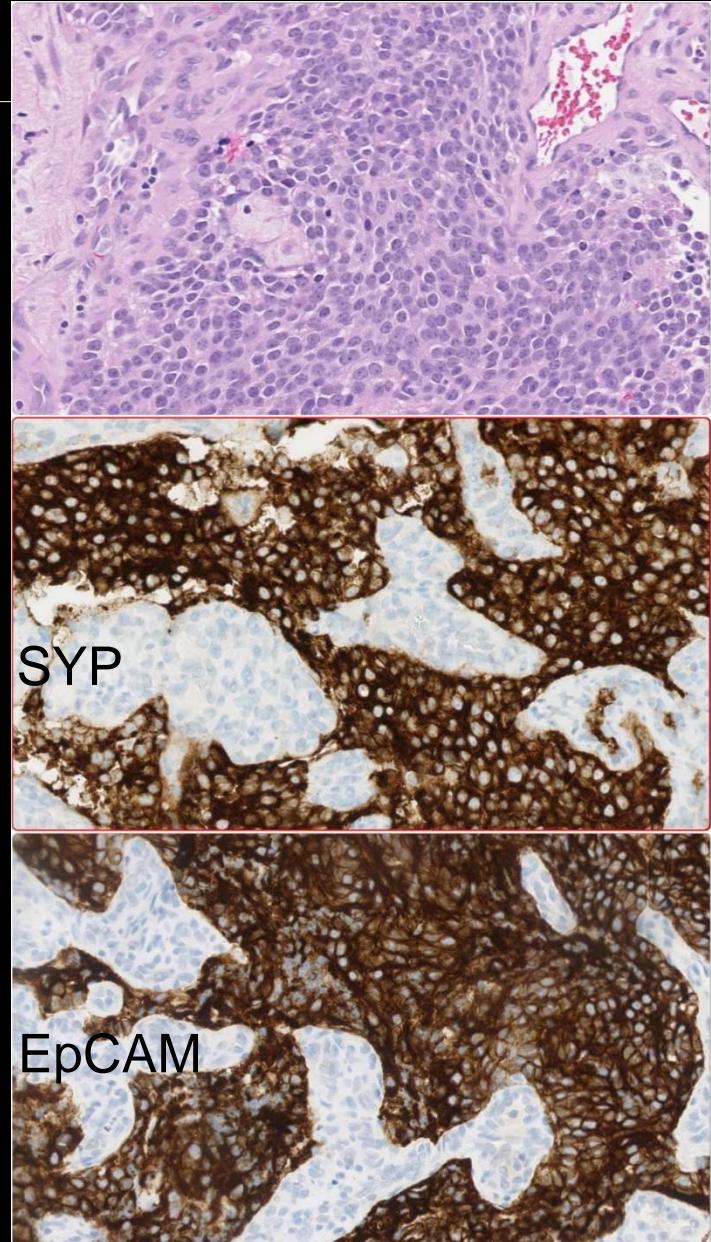
Often upgraded in malignancies

+(-)

- Adenocarcinomas (of most types)
- Neuroendocrine neoplasms

+/-

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



Olfactory neuroblastoma

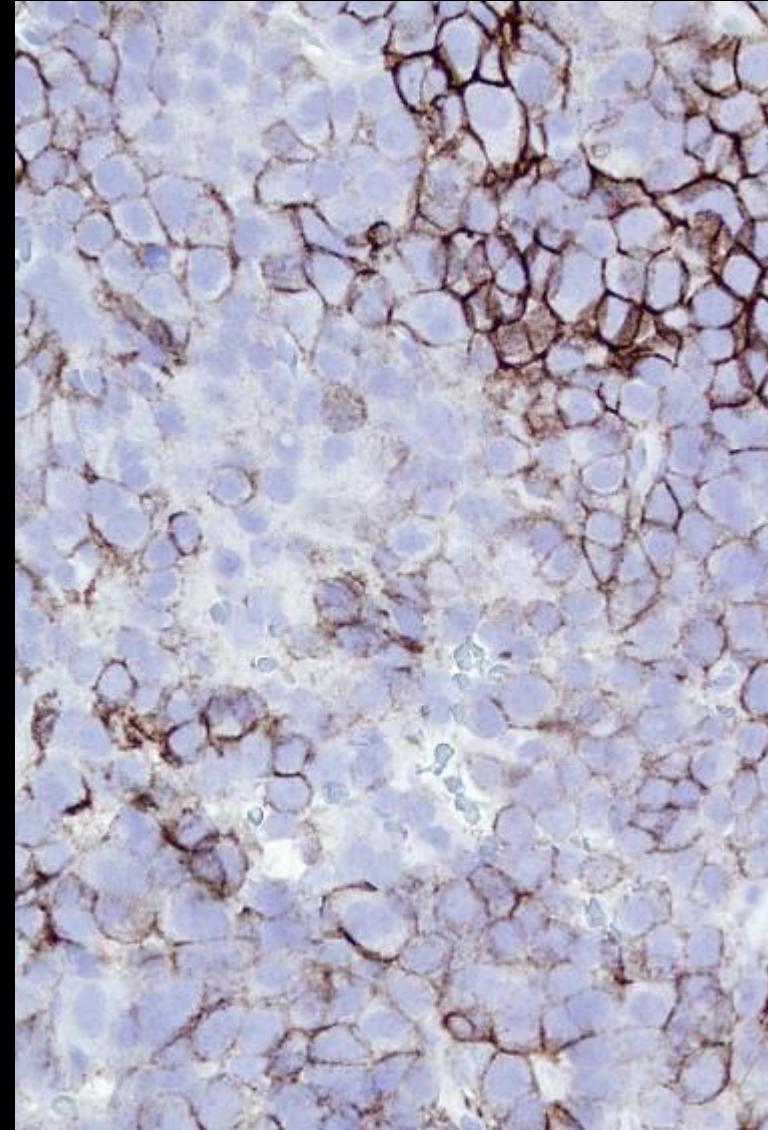
Ep-CAM

-/+

- Lobular breast carcinoma
- Hepatocellular carcinoma
- Squamous cell carcinoma
- Renal cell carcinoma
- Malignant mesothelioma

-

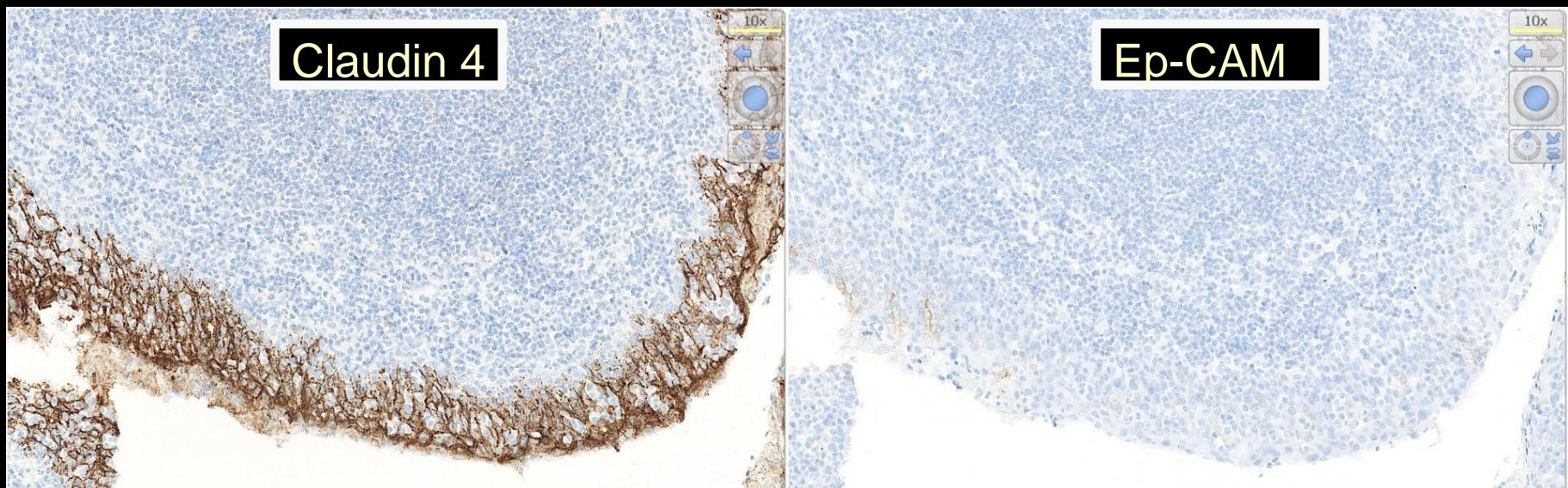
- Adrenal cortical carcinoma
- Choroid plexus carcinoma
- Sarcomas (apart from synovial)
- Lymphomas



HCC

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

20x

20x

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):

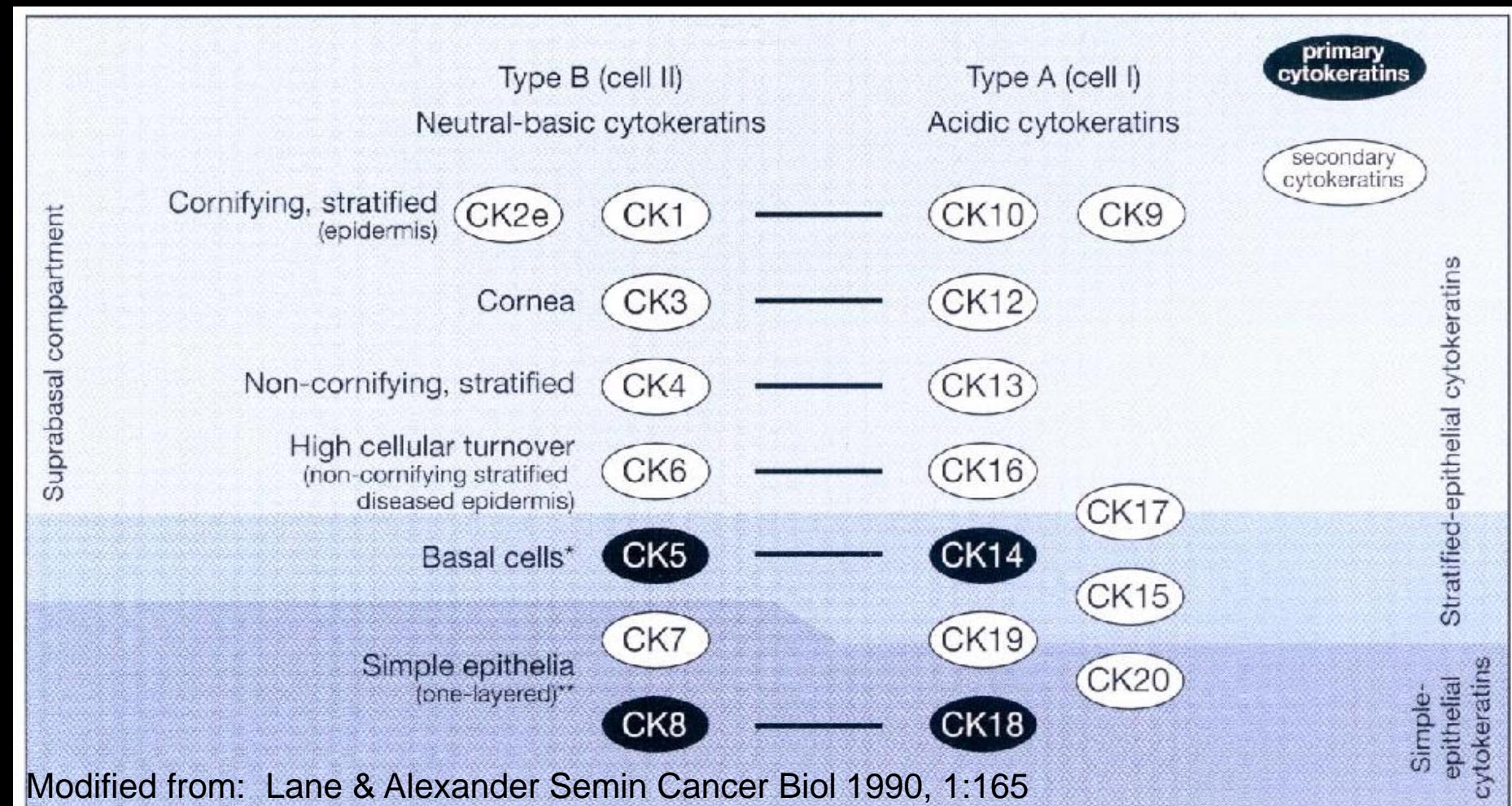
- CK9 (64 kDa) - CK20 (40 kDa)

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



Modified from: Lane & Alexander Semin Cancer Biol 1990, 1:165

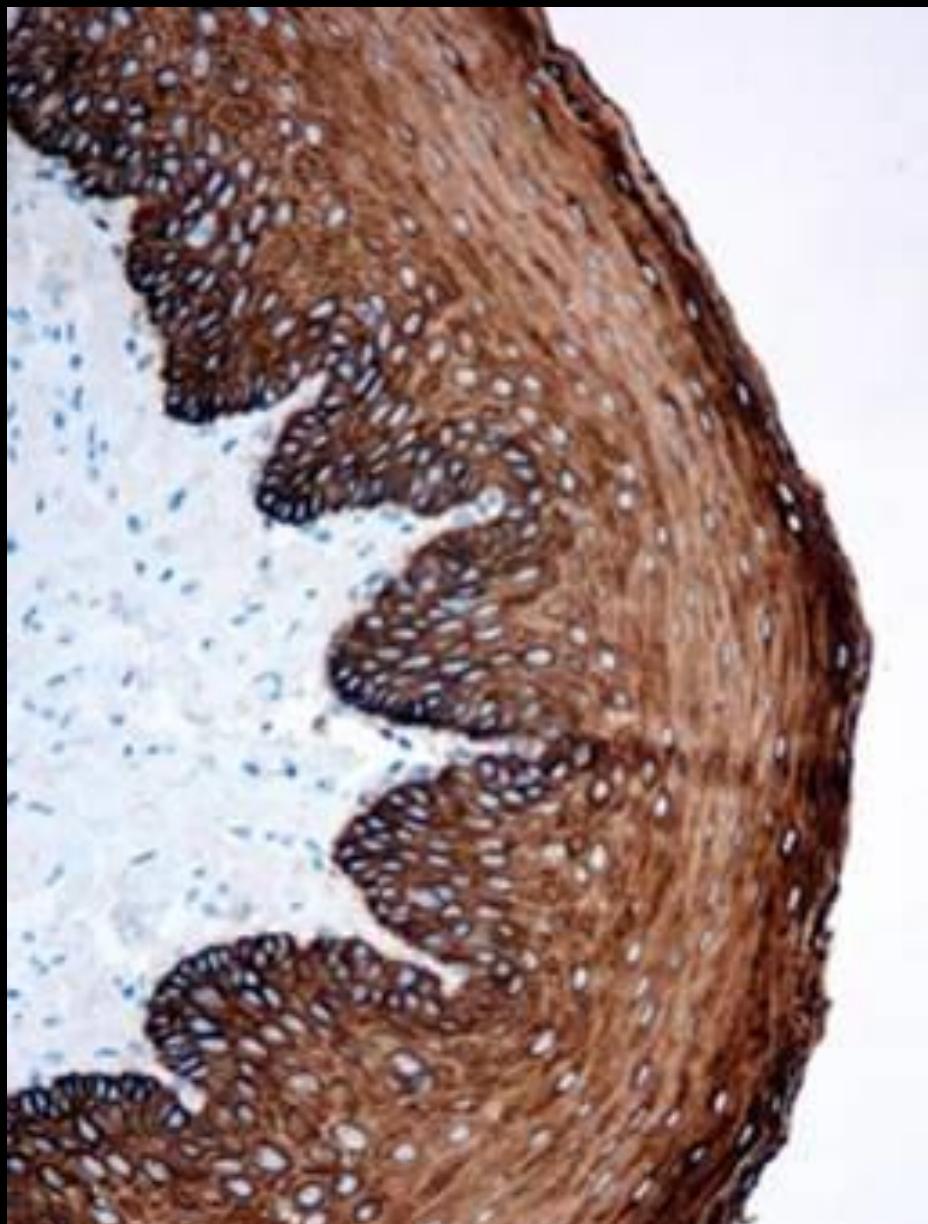
Cytokeratin types and cell types

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 thyro.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

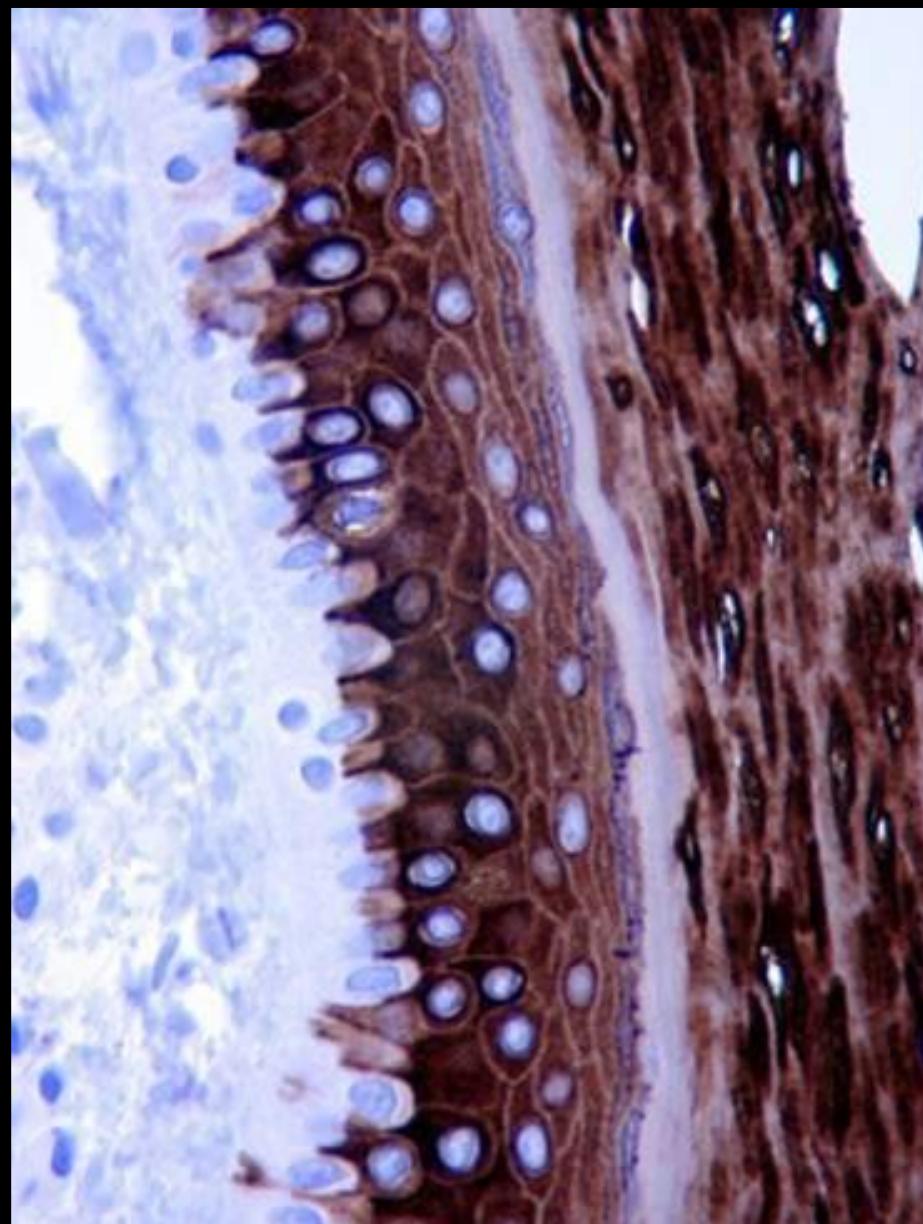
HMW Cytokeratin types - squamous epithelia

Neutral/Basic (B, class II)	1 10	4	13	5	14	17	19	7	20	8 18
Acidic (A, class I)										
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 thyro.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

HMW Cytokeratin types - squamous epithelia



CK5: esophagus

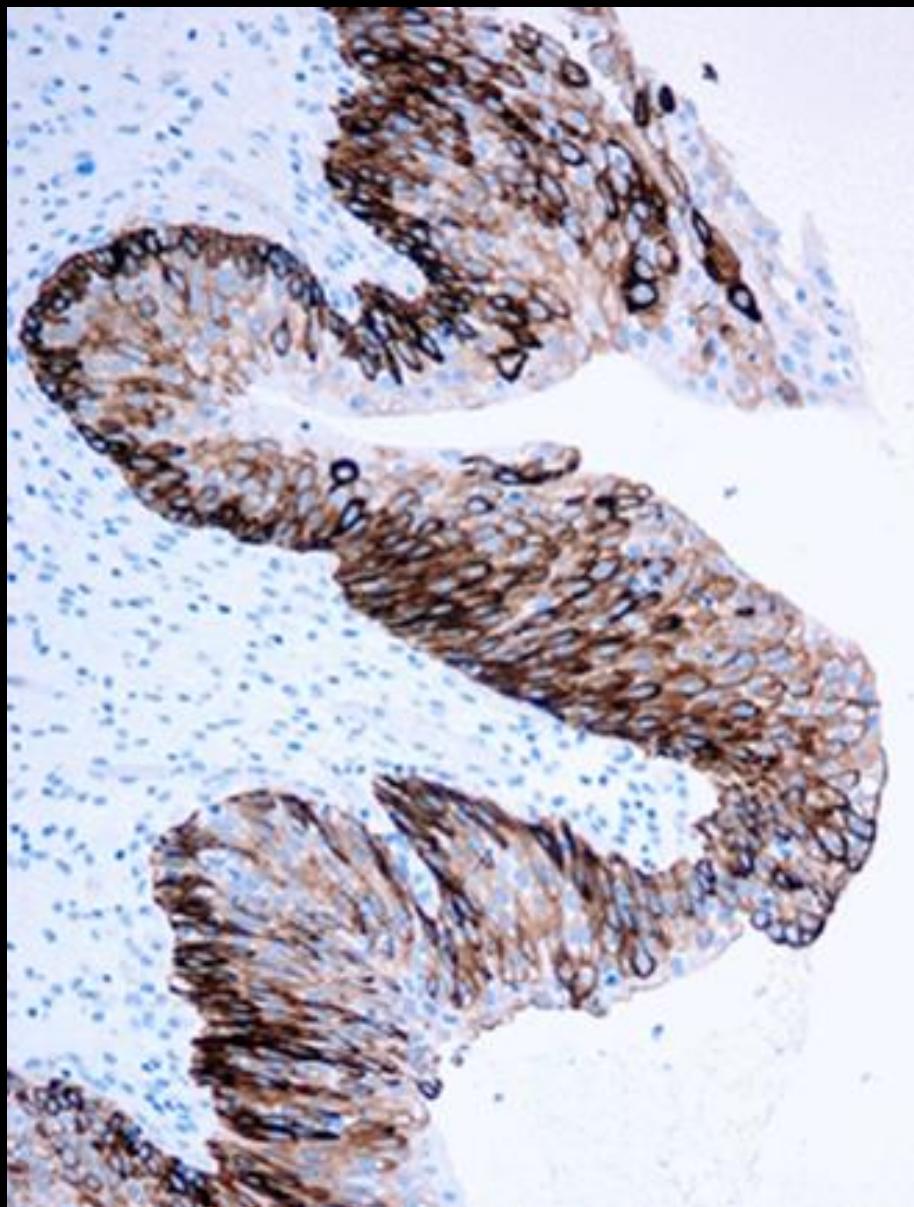


CK4: esophagus

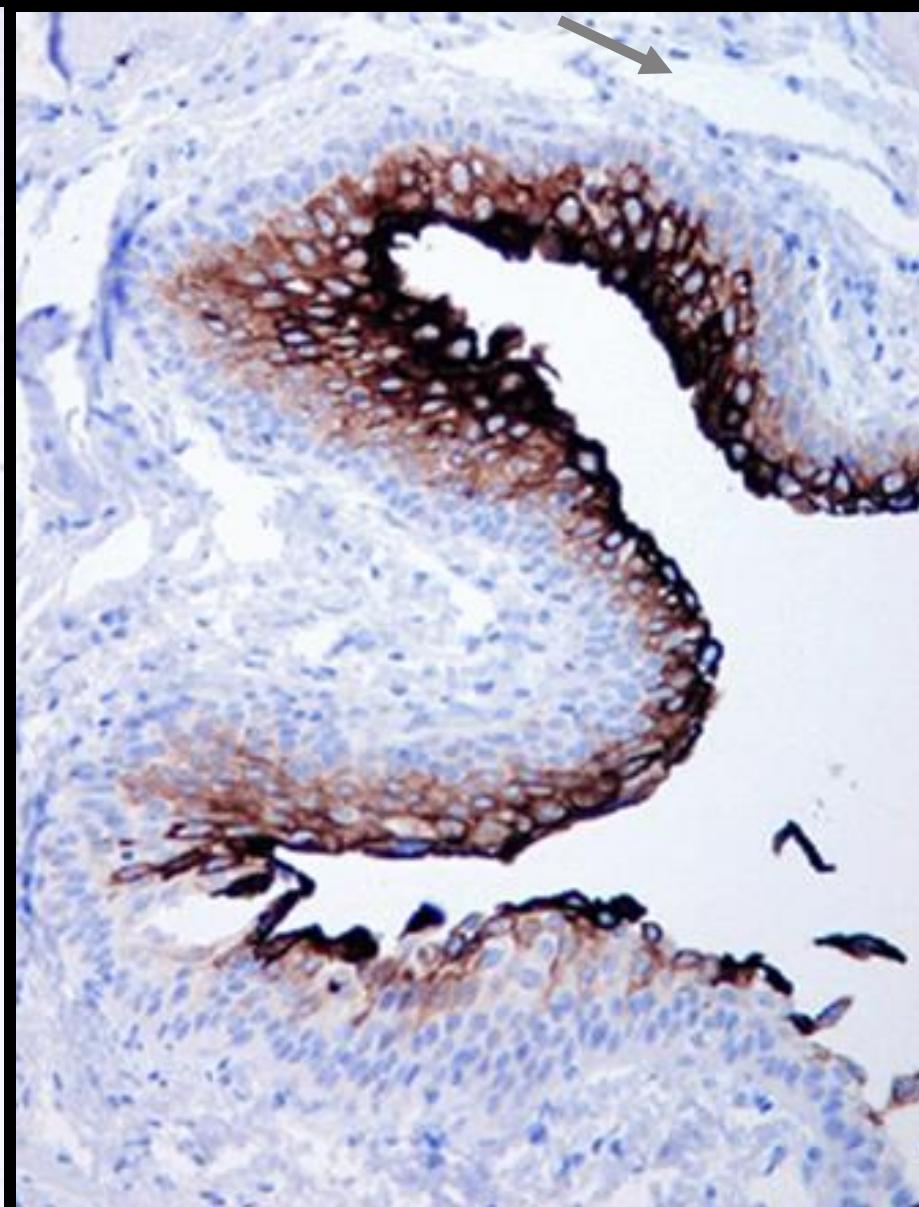
Cytokeratin types - urothelium

	1	4	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10								
Acidic (A, class I)									
Squamous epithelia:									
- suprabasal, keratinizing	+++	-	-	+	++	(+)	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	+++	+++	(+) ¹	(++) ¹²	(+) 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 thyro.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-

Cytokeratin types - urothelium



CK5 (+CK13)

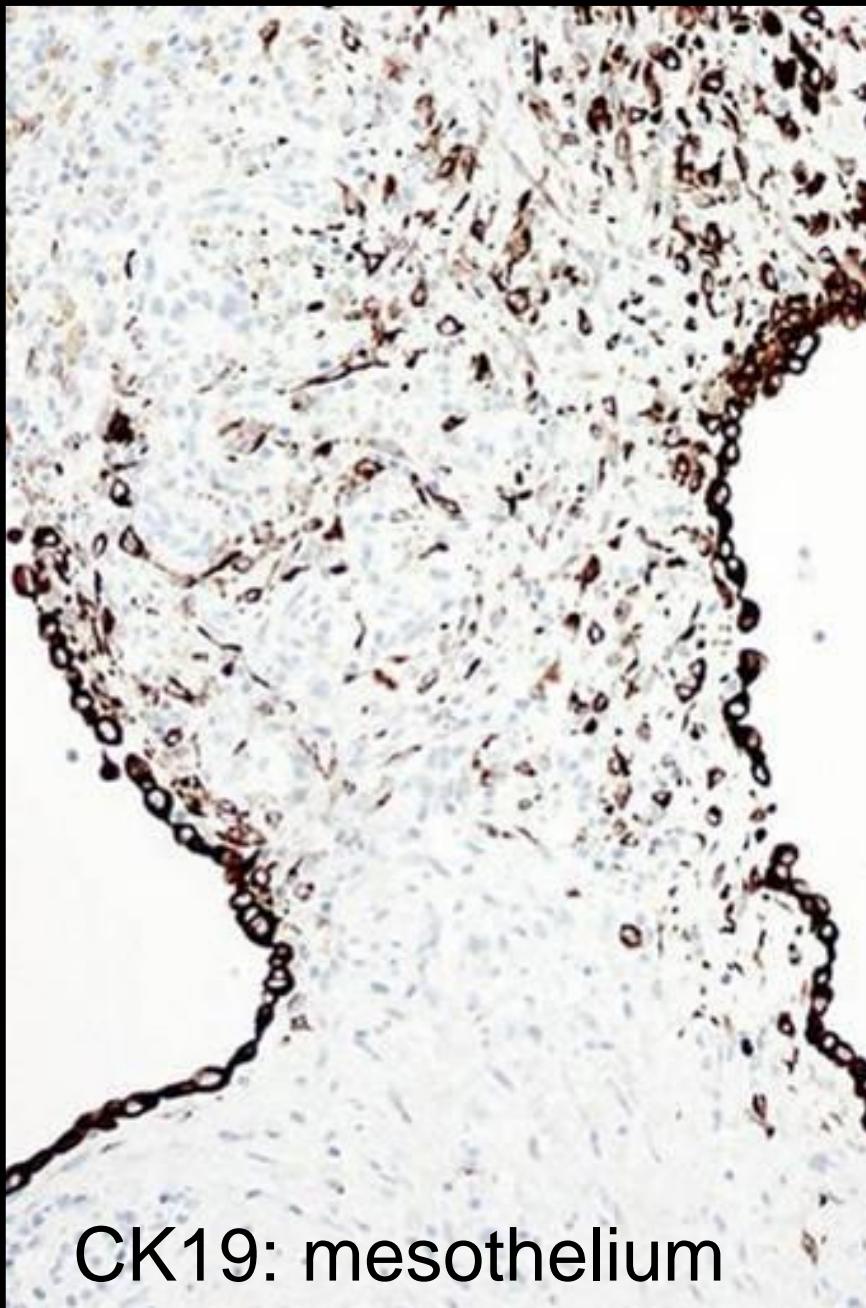


CK20

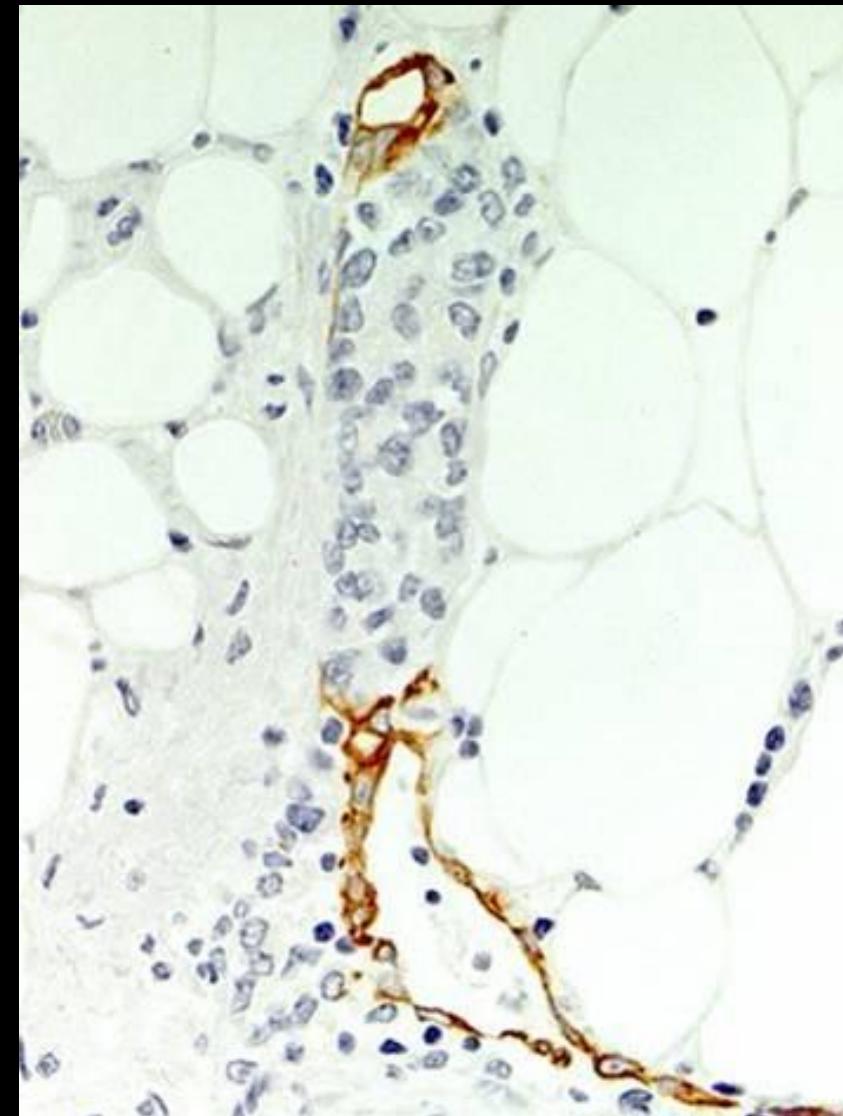
Cytokeratin types - mesothelium

	1	4	13	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10									
Acidic (A, class I)										
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

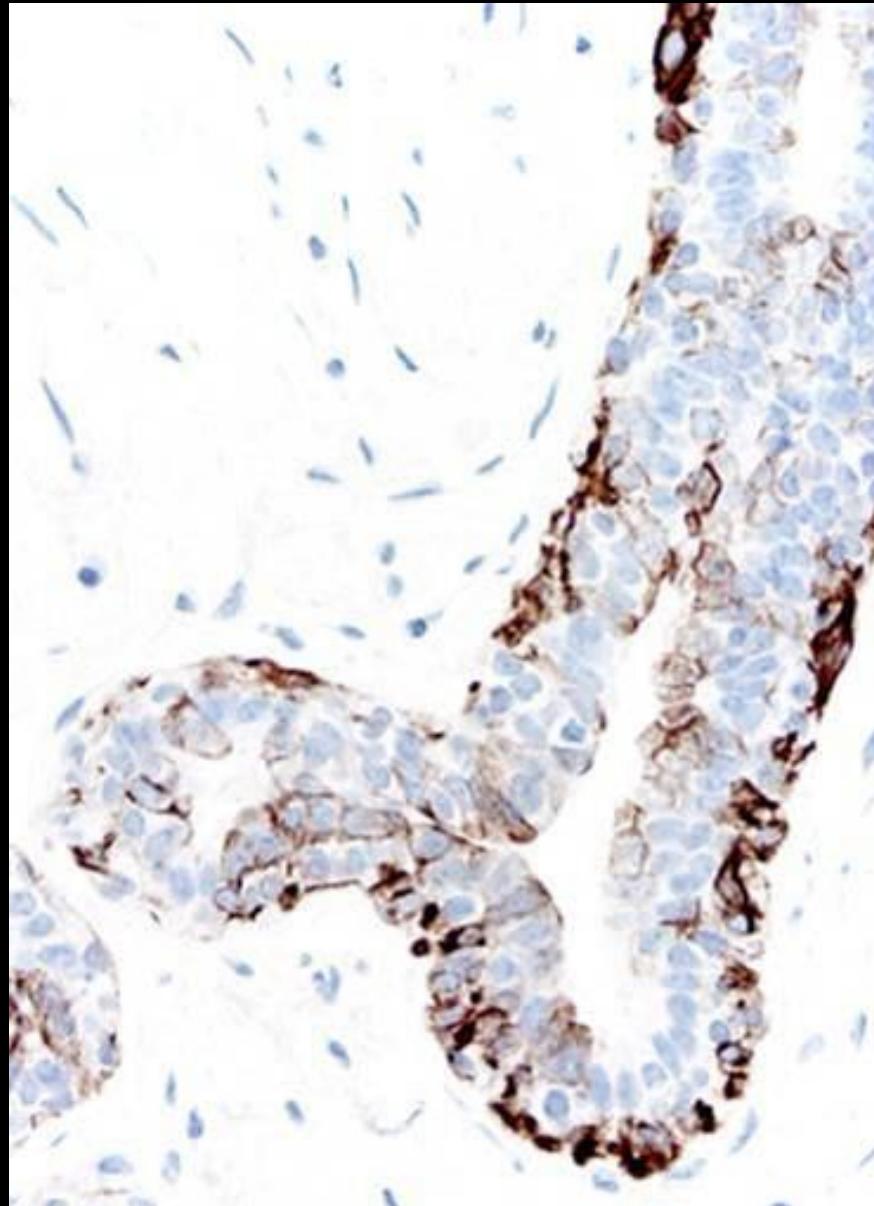


CK5: mesothelium
(adenocarcinoma neg.)

Cytokeratin types - complex epithelia

	1	4	13	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10									
Acidic (A, class I)										
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 thyro.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - complex epithelia



CK5 (14,17): breast

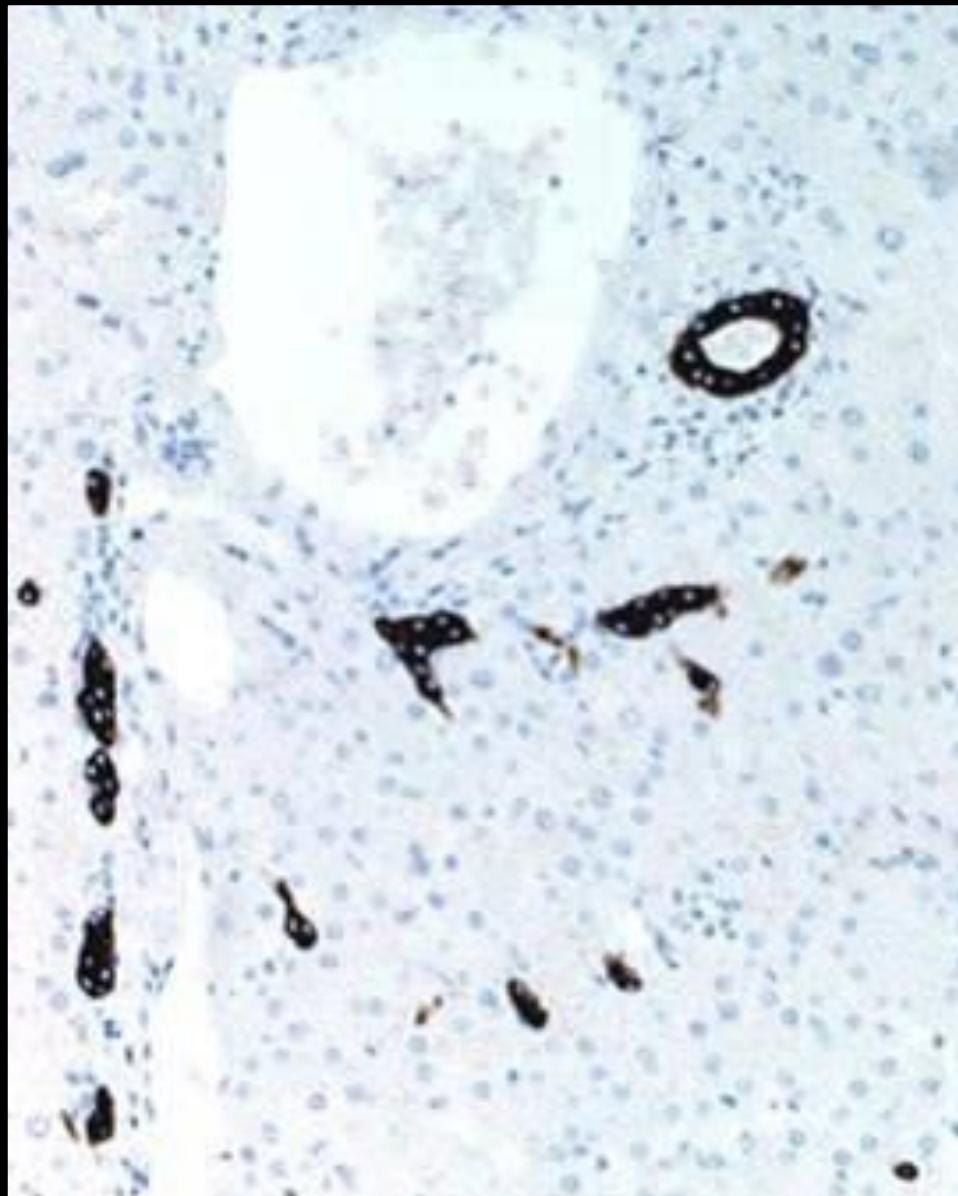


CK18 (8,7): breast

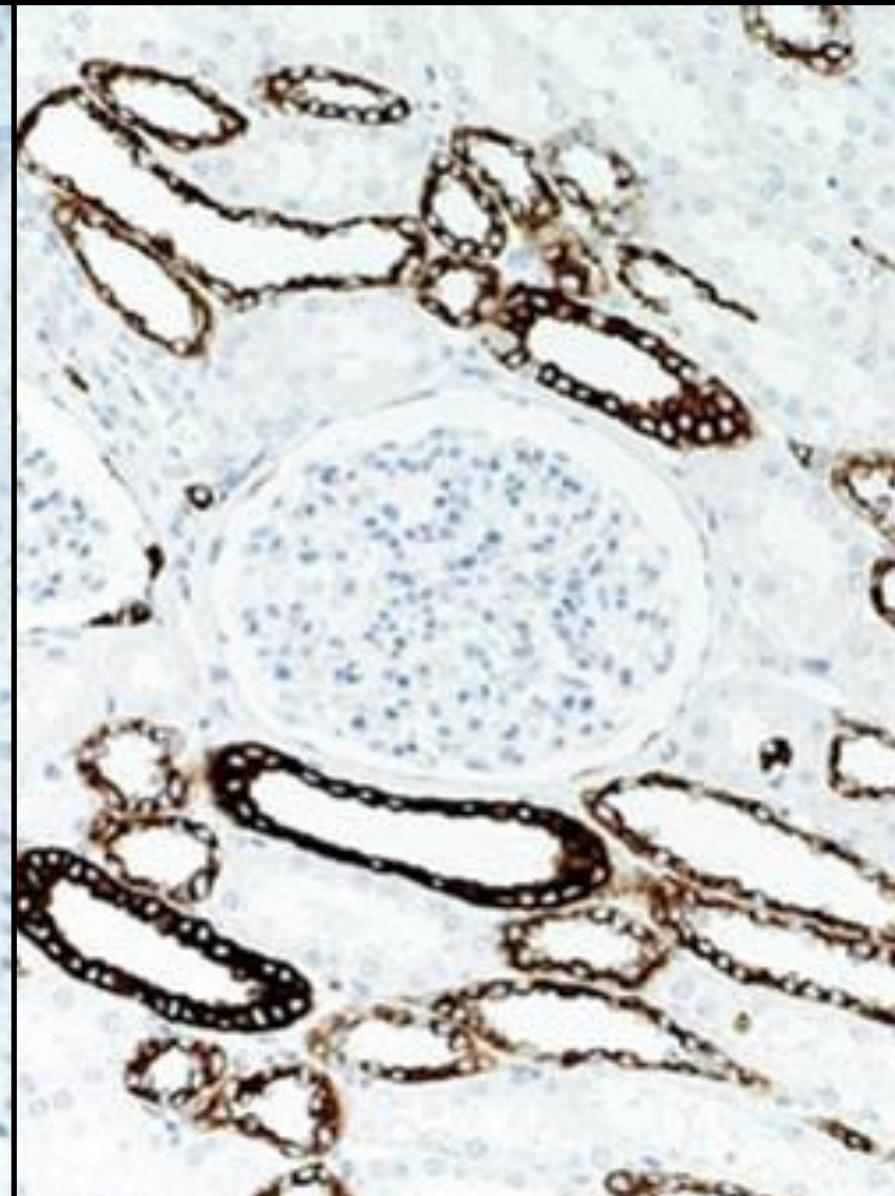
Cytokeratin types - simple epithelia

	1	4	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10								
Acidic (A, class I)									
Squamous epithelia:									
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) 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 thyro.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-

Cytokeratin types - simple epithelia (liver, kidney)



CK7(19): bile ducts

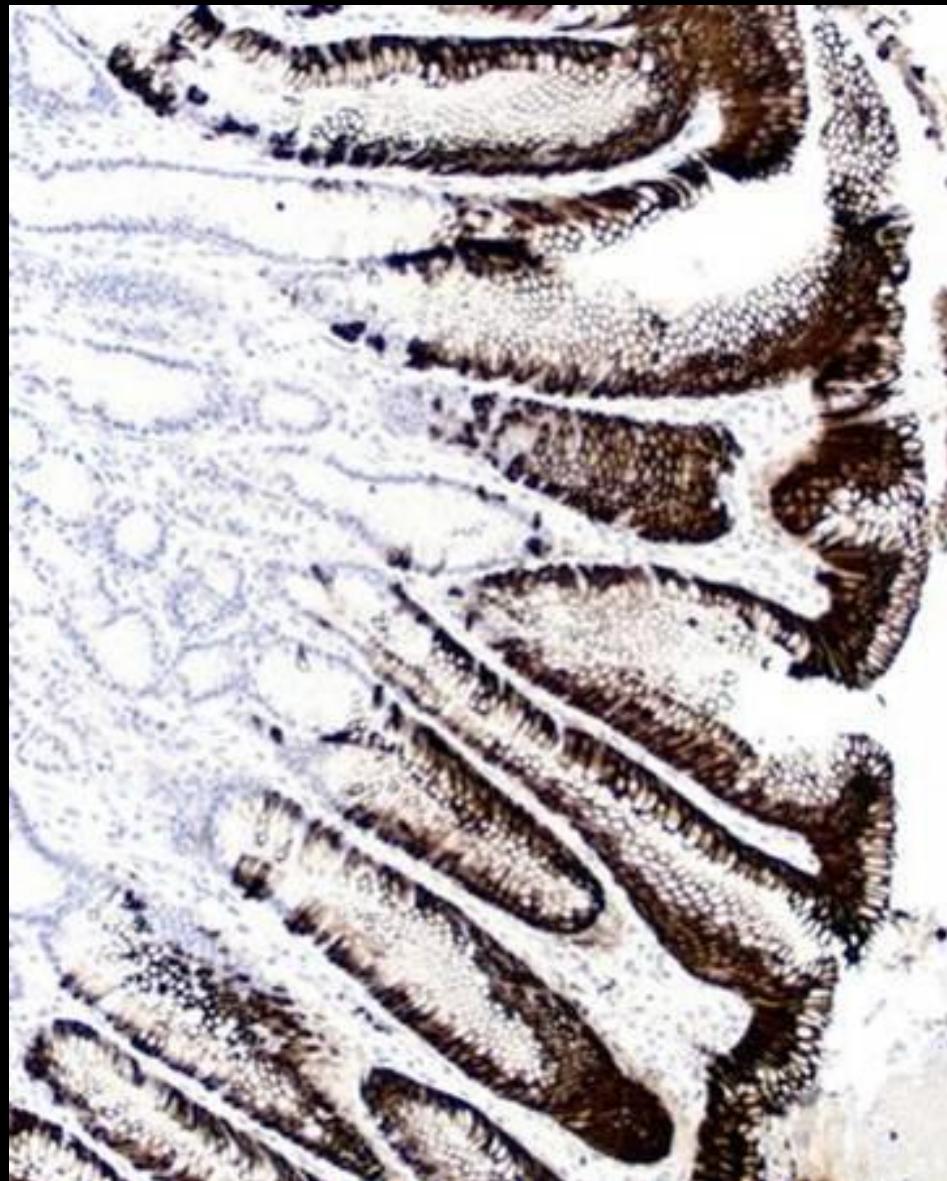


CK7(19): renal col.

Cytokeratin types - simple epithelia

	1	4	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10								
Acidic (A, class I)									
Squamous epithelia:									
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) 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	-	-	-	-	-	-	+++	+++	-
⁴Stomach (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

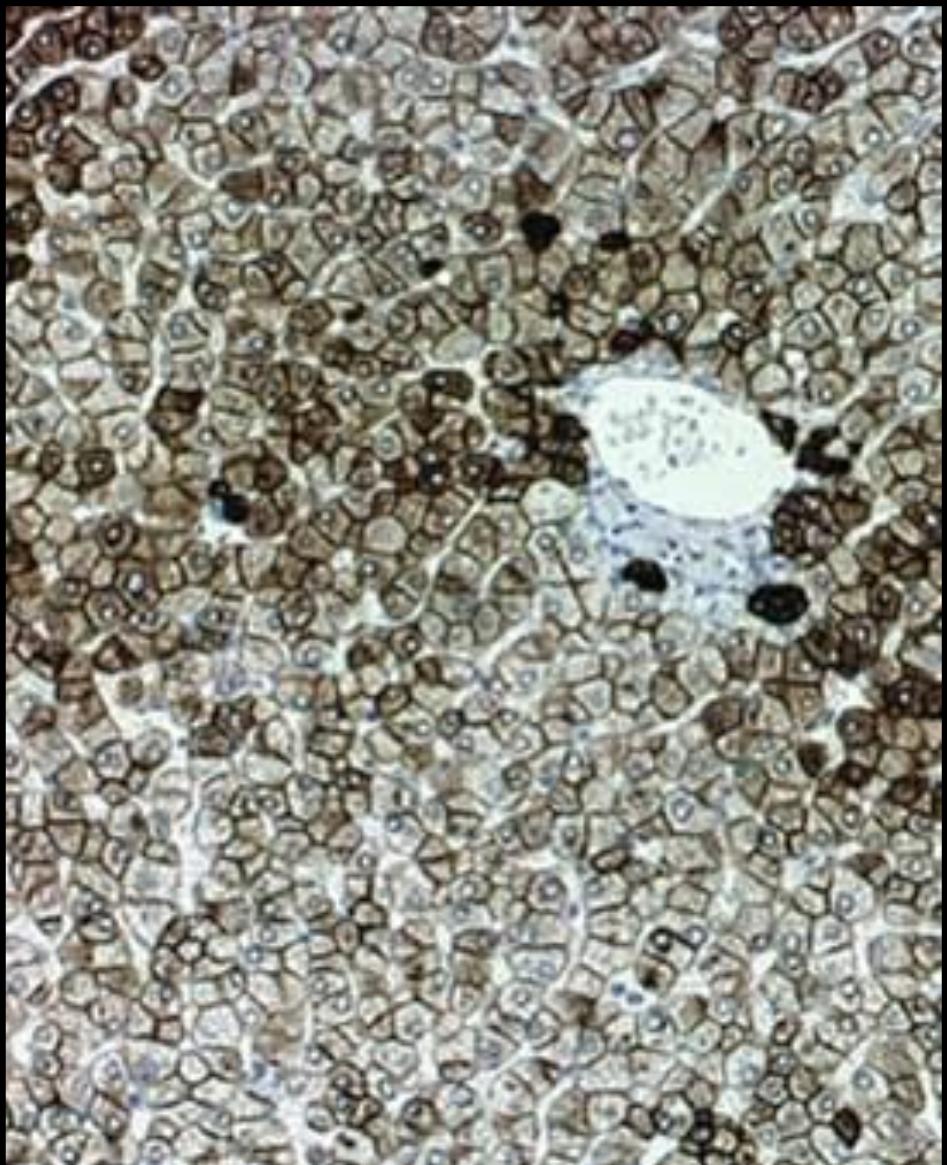


CK20: colon

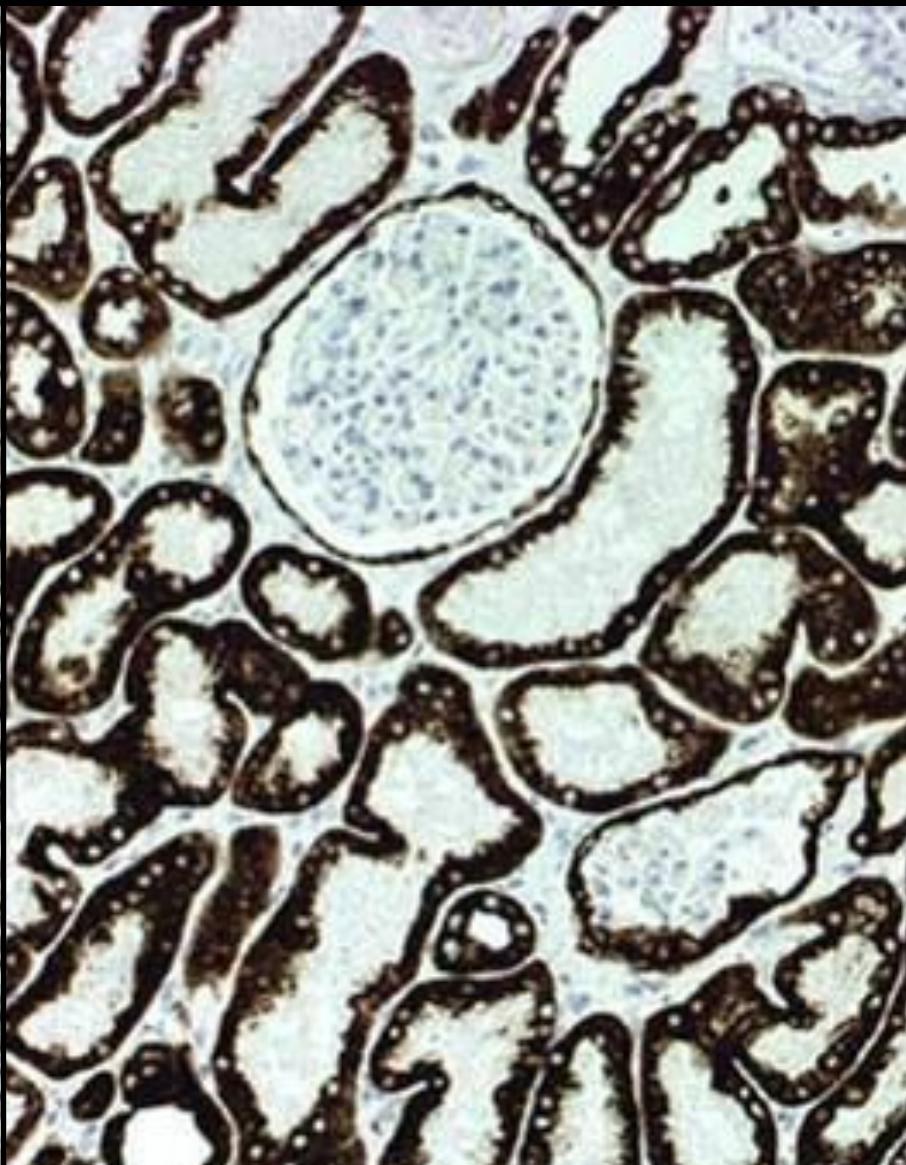
Cytokeratin types - simple epithelia

	1	4	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10								
Acidic (A, class I)									
Squamous epithelia:									
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) 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 thyro.)	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-

Cytokeratin types - simple epithelia



CK8: liver



CK8: kidney

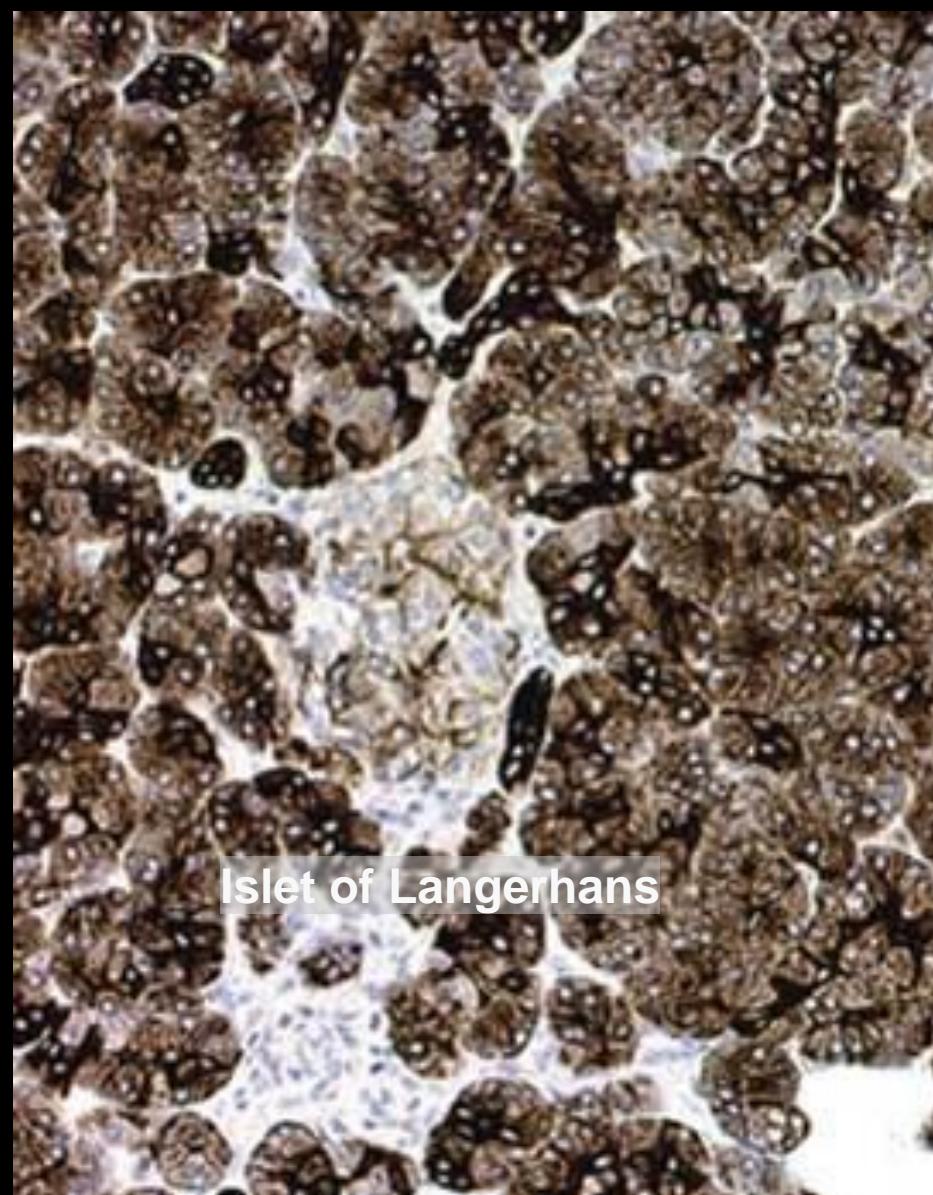
Cytokeratin types - simple epithelia

	1	4	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10								
Acidic (A, class I)									
Squamous epithelia:									
- suprabasal, keratinizing	+++	-	-	+	++	-(+)	-	-	-
- suprabasal, non-keratinizing	+	+++	+++	+	++	(+)	-	-	-
- basal cells (¹ tonsil, ² mucosa)	-	-	-	-	+++	-(+) ¹	(++) ¹²	-(+) 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 (⁵Merkel, ⁶thyro.)	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷ sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-

Cytokeratin types - simple epithelia



CK20: Merkel cells



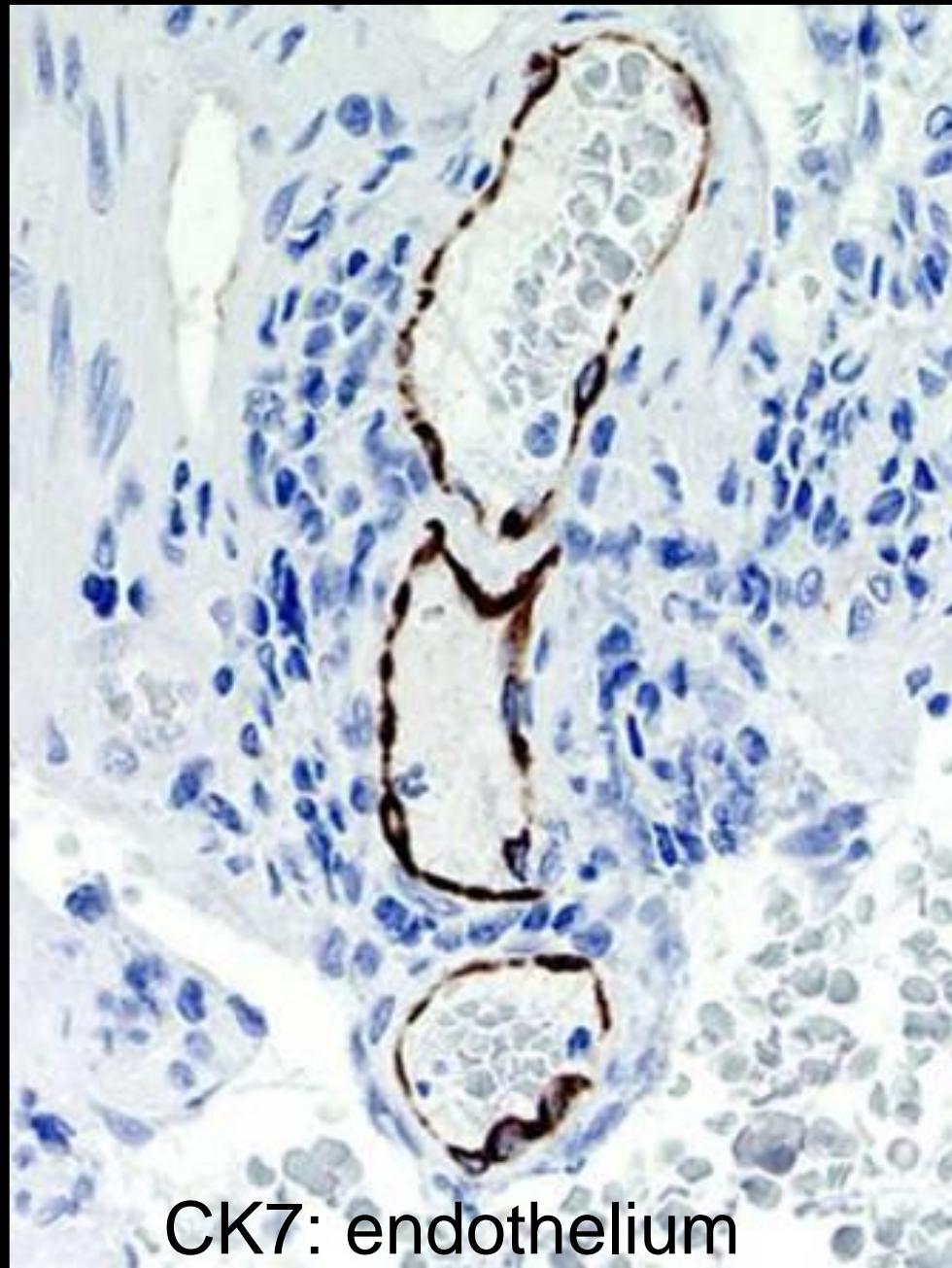
CK8: Pancreas

Islet of Langerhans

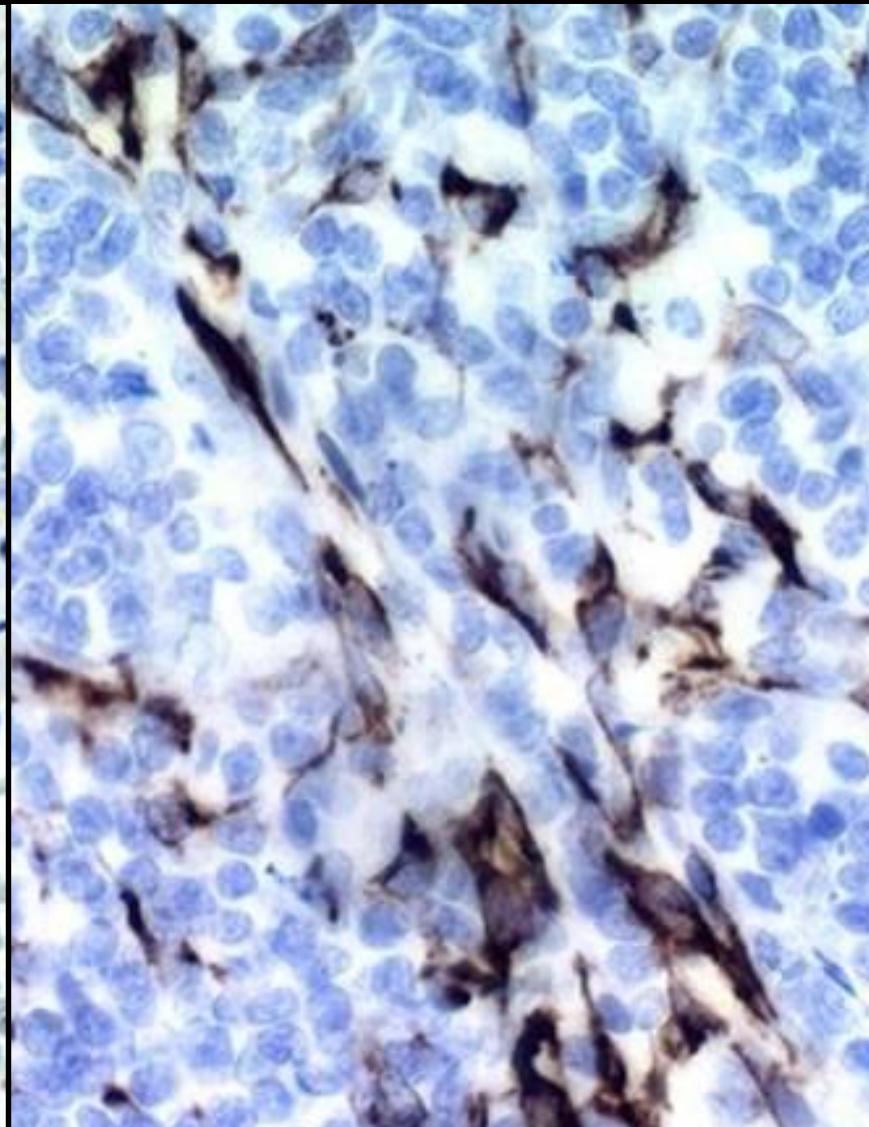
Cytokeratin types - mesenchymal cells

	1	4	13	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)	10									
Acidic (A, class I)										
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 thyro.)	-	-	-	-	-	-	(+++) ⁵	(++) ⁶	(+++) ⁵	+++
Smooth muscle (vasc., myom.), myofibrobl., ⁷sm.ves.endothelia	-	-	-	-	-	-	+	(++) ⁷	-	++

Cytokeratin types - mesenchymal cells



CK7: endothelium



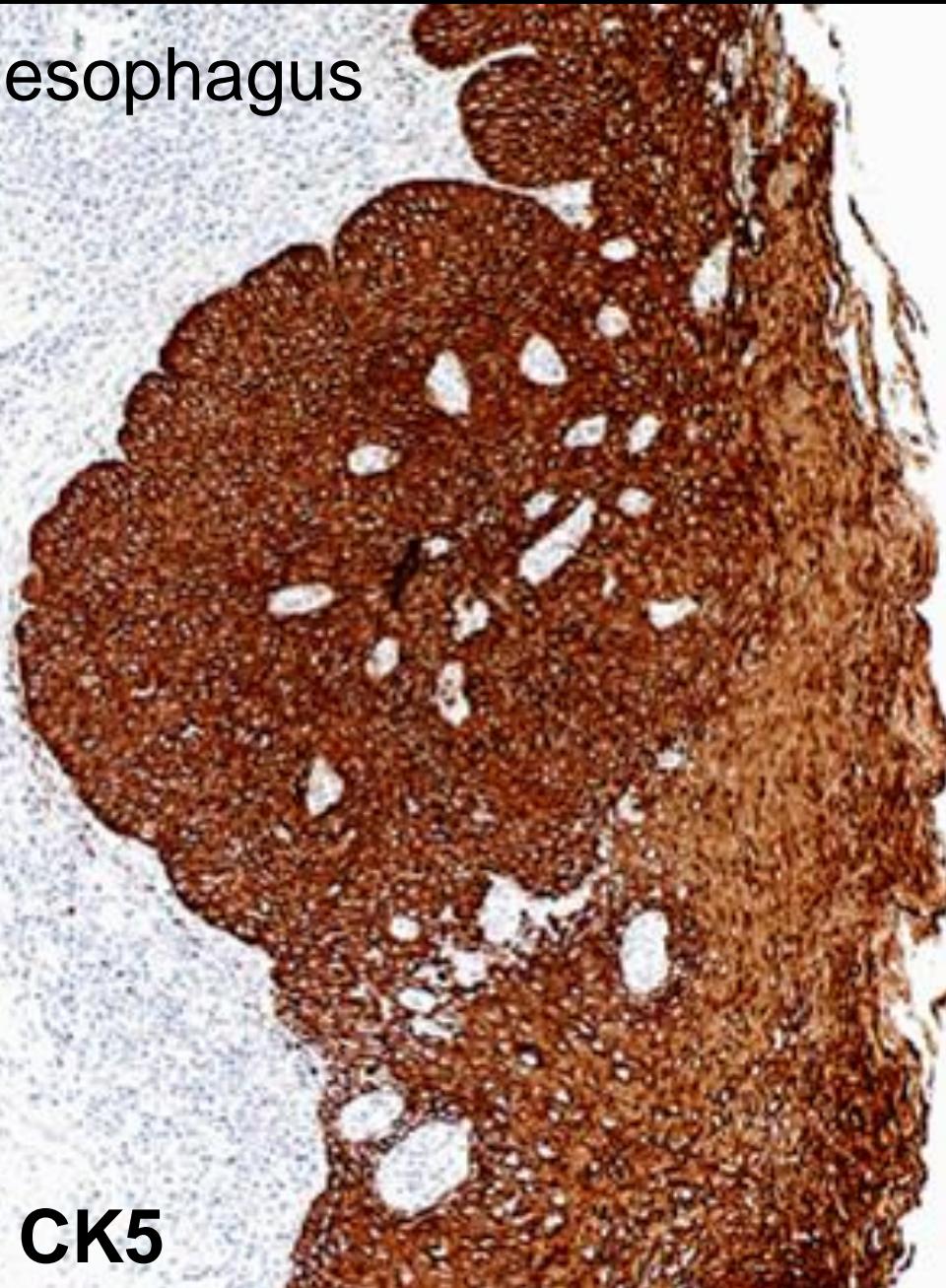
CK8: lymph node
fibroblastic reticulum cells

Cytokeratins in squamous cell carcinoma

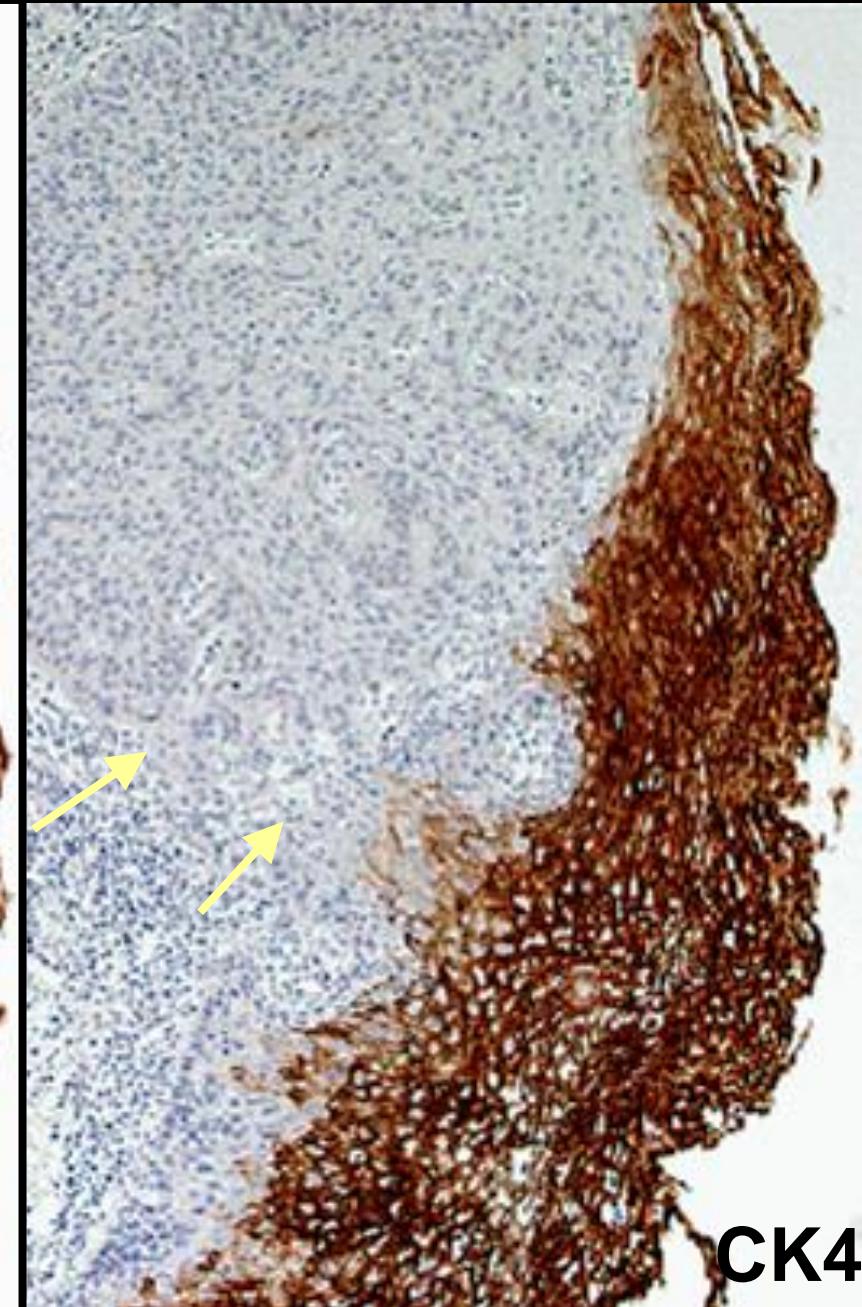
	1	4	13	5	14	17	19	7	20	8
Neutral/Basic (B, class II)	10									18
Acidic (A, class I)										
Squamous cell carcinoma	+	+	+	++	++	+	+	+	-	+
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epithelia (lung, breast)	-	-	-	(+)	(+)	(+)	++	++	-	++
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

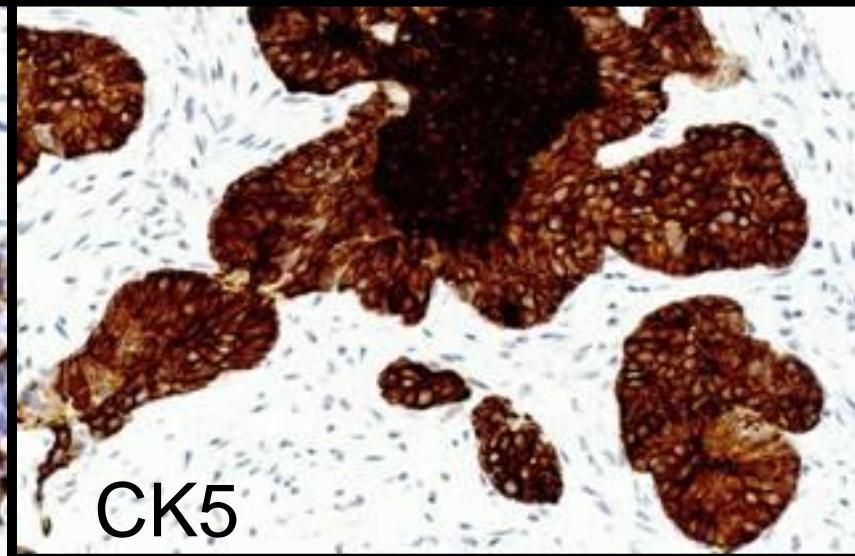
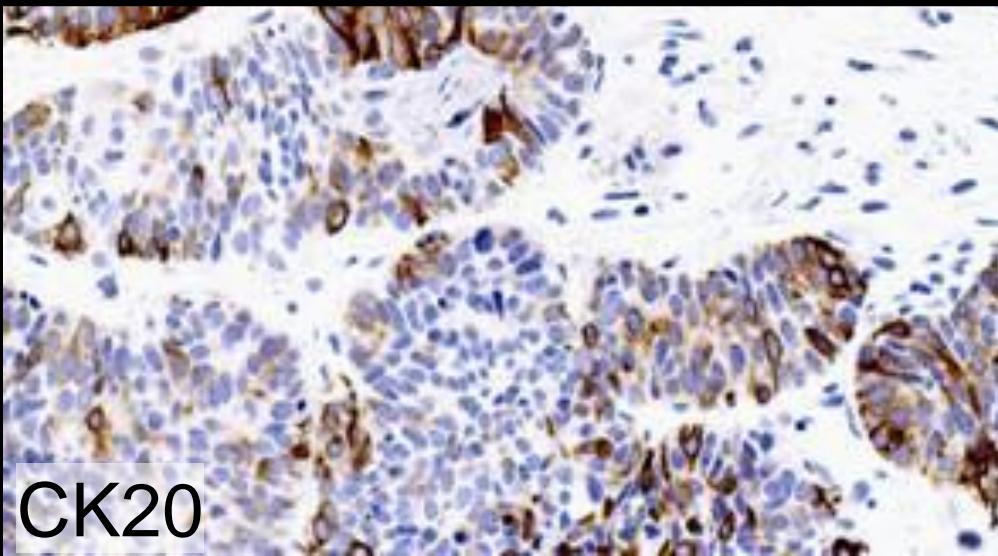
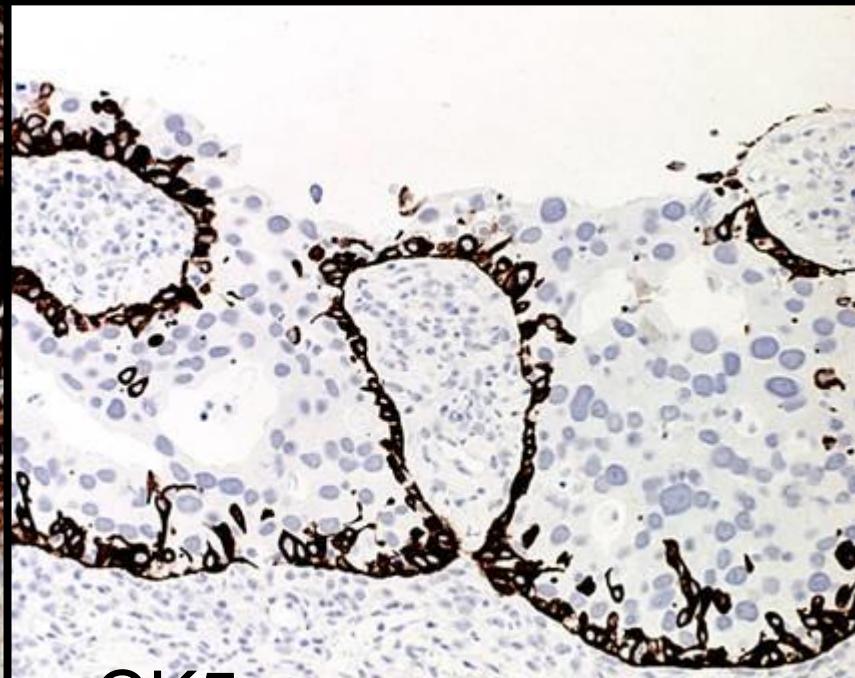
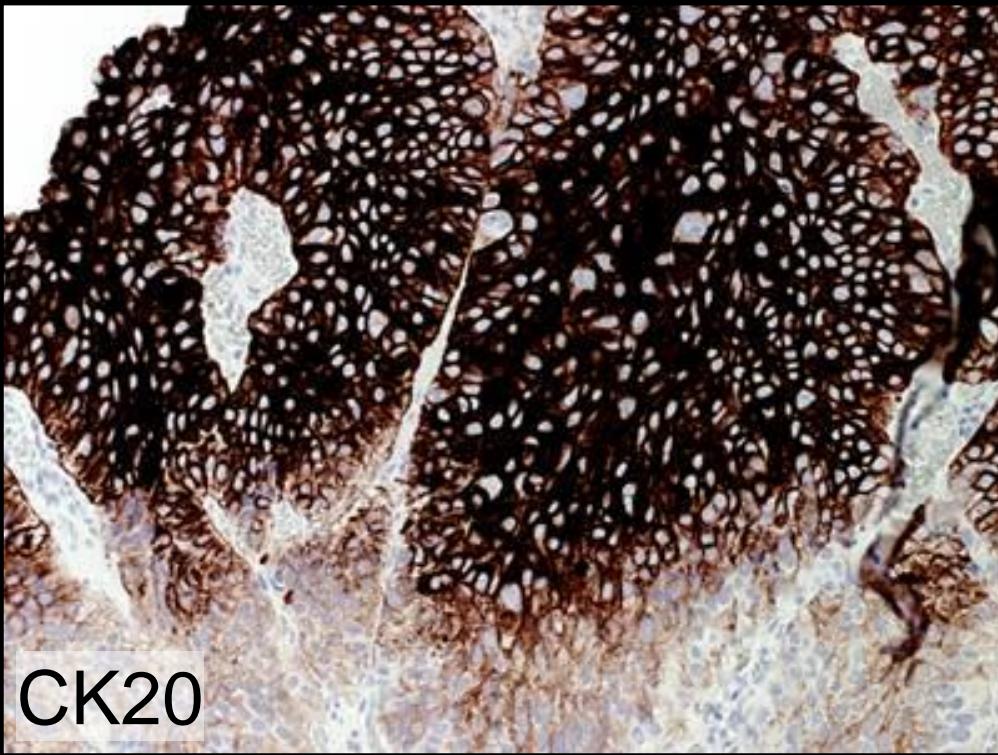


CK4

Cytokeratins in urothelial carcinoma

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

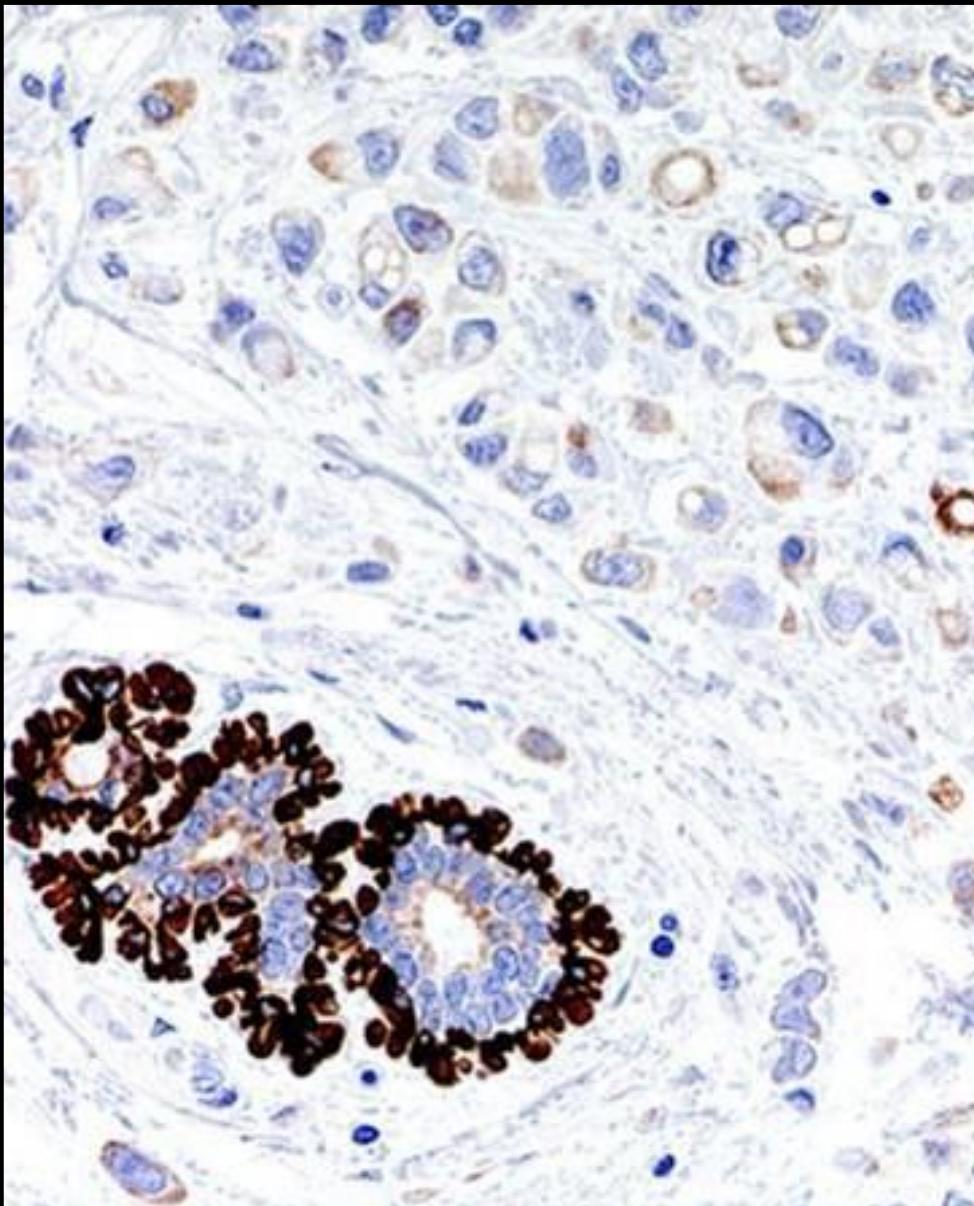
Cytokeratins in urothelial carcinoma



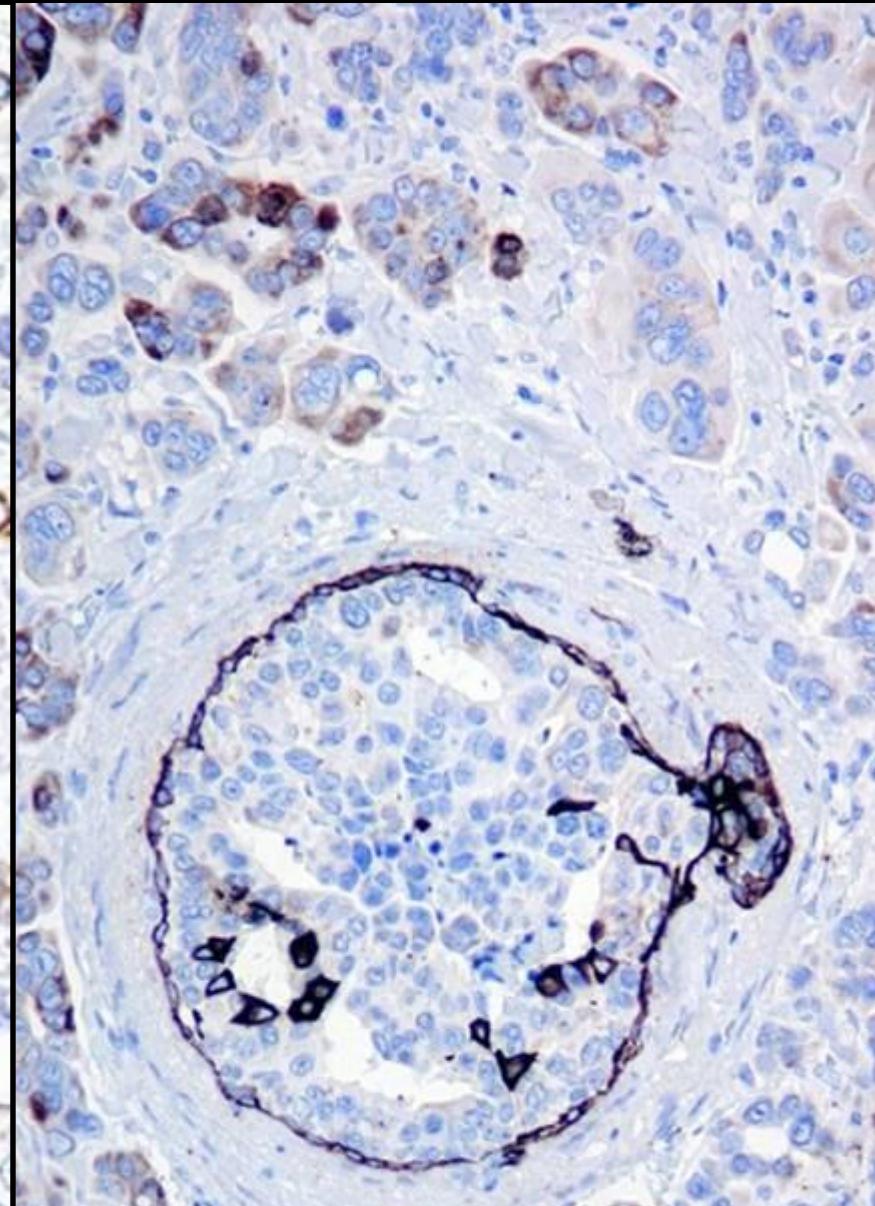
Cytokeratins in adenocarcinomas

	1 10	4	13	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)										
Acidic (A, class I)										
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epith. (lung, breast)	-	-	-	(+)	(+)	(+)	++	++	-	++
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



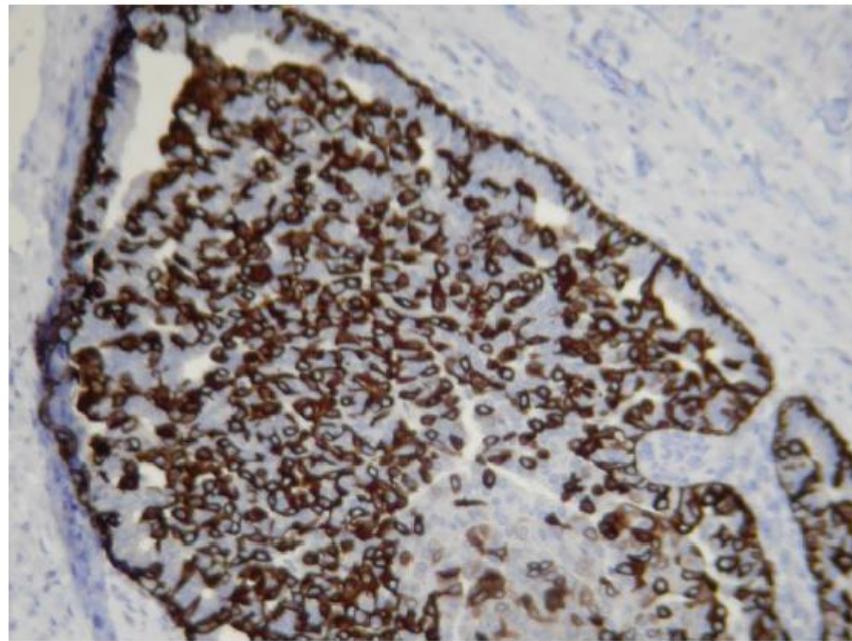
CK5: Breast lob. carcinoma



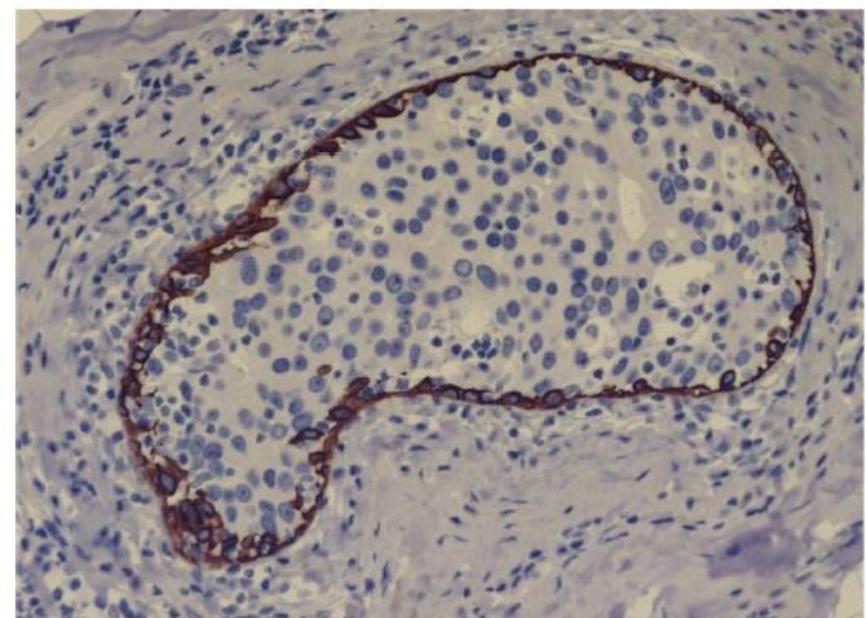
CK5: Breast duct. carc.

Ductal Carcinoma In Situ

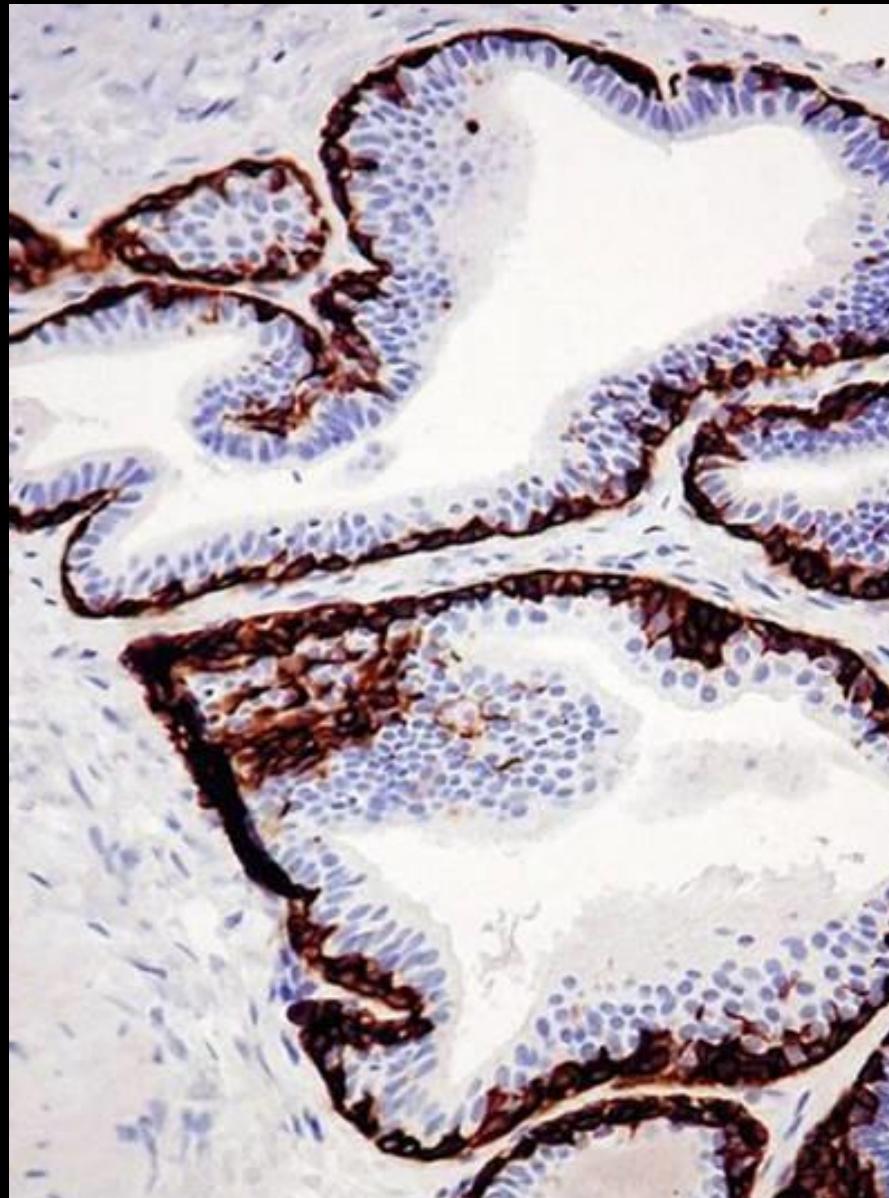
CK14 Ductal Hyperplasia (UDH)



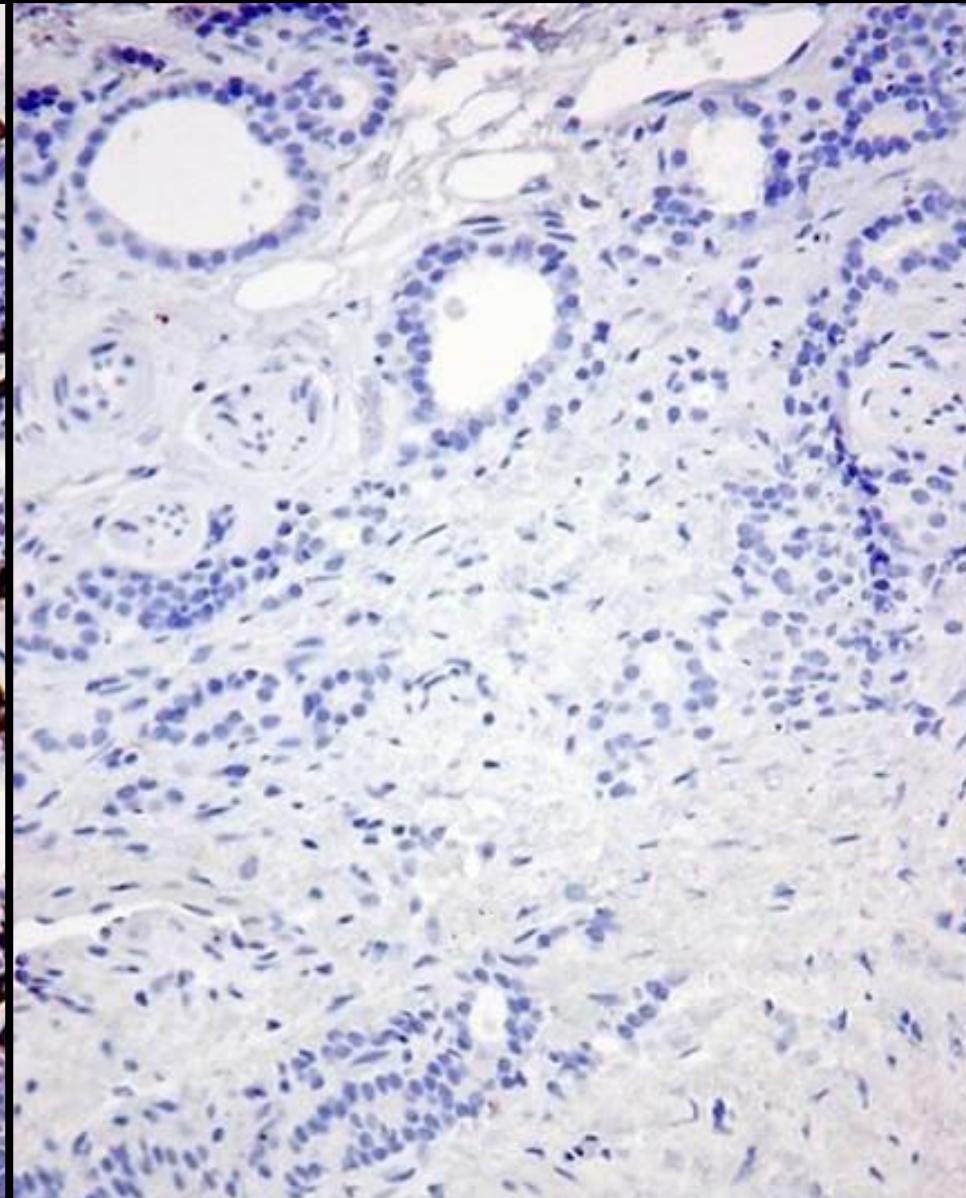
CK14 Ductal Carcinoma In Situ



Cytokeratins in adenocarcinomas



CK5: Prostate hyperplasia

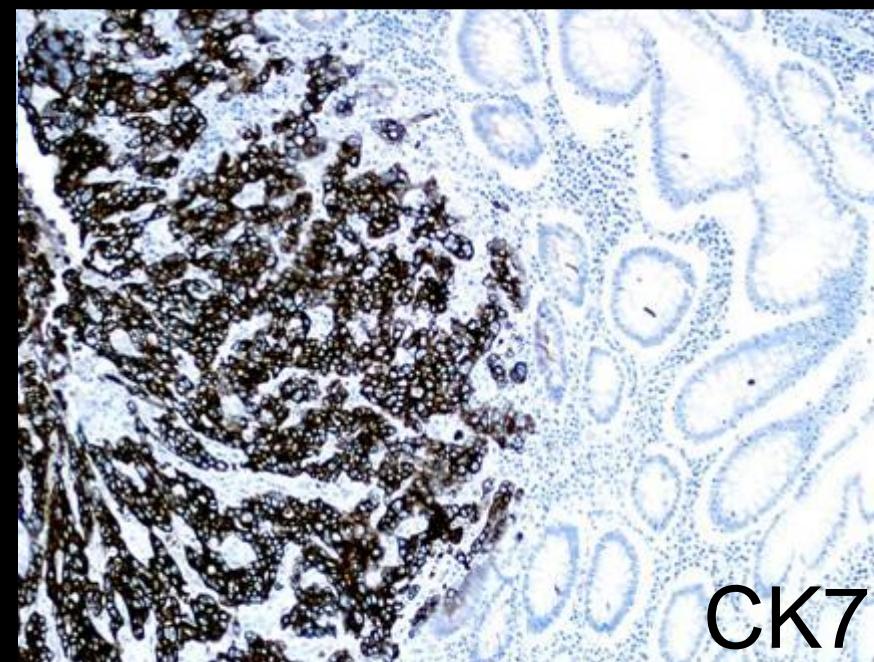
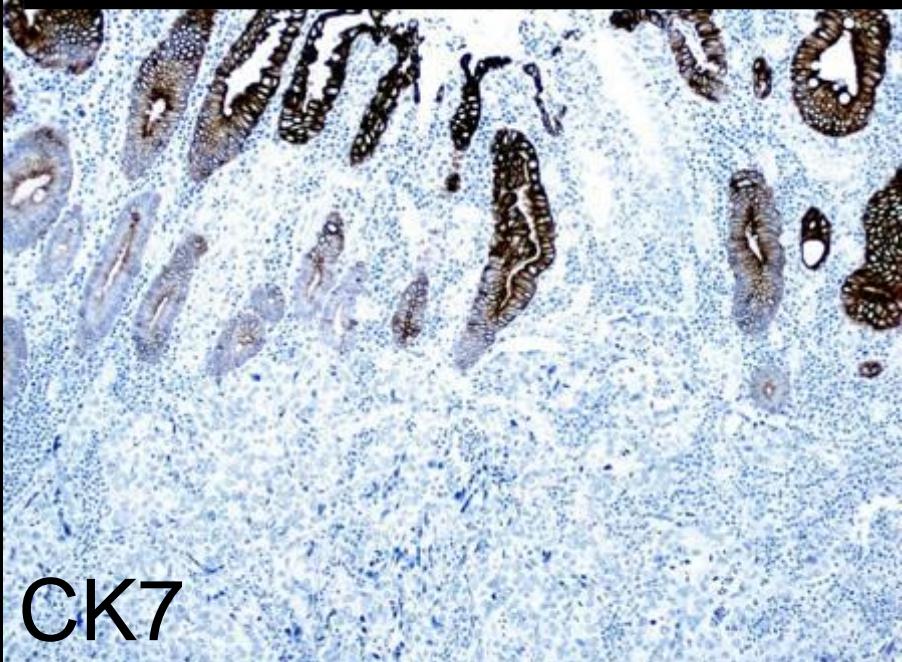
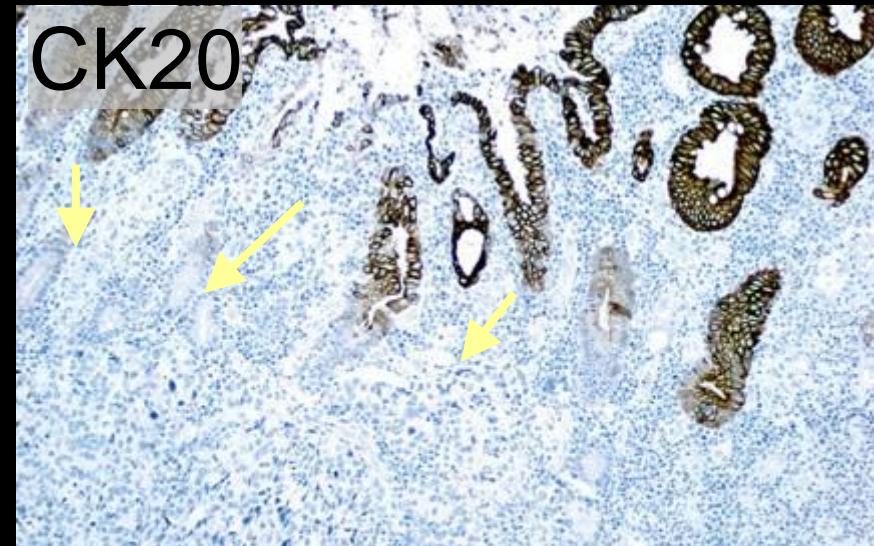
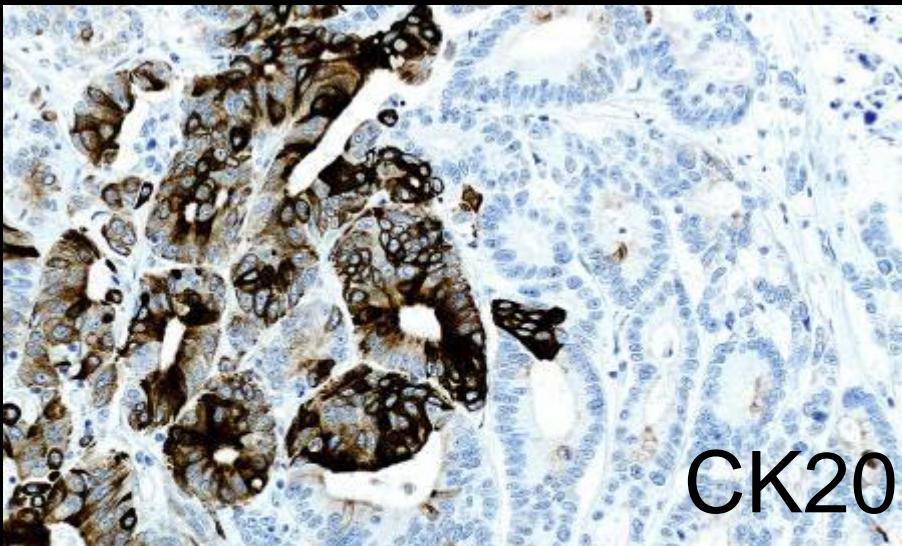


CK5: prostate adenocarc.

Cytokeratins in adenocarcinomas

	1 10	4	13	5	14	17	19	7	20	8 18
Neutral/Basic (B, class II)										
Acidic (A, class I)										
Squamous cell carcinoma	(+)	+	+	++	++	(+)	(+)	(+)	-	(+)
Transitional cell tumour	-	+	+	+	+	+	++	++	++	++
Malignant mesothelioma	-	-	-	++	++	+	++	+	-	++
Adenocarcinoma: complex epith. (lung, breast)	-	-	-	(+)	(+)	(+)	++	++	-	++
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

Secondary panels for ‘**carcinoma**’ identification/subclassification

- Apart from cytokeratins and "general epithelial markers" (EpCAM, Cl4)
- "GI-markers" CDX2, CAD17, SATB2, SMAD4, CEA
- "Fem.gen.tract markers" CA125, PAX8, WT1, ER, p53
- "Liver cell markers" Arginase, Glypican3, GlutSynt, canCD66a, canCD10, AFP
- Neuroendocr. markers Synaptophysin, Chromogranin
- "Breast markers" GATA3, ER, GCDFP15, Mam.glob.

Secondary panels for **carcinoma** identification/subclassification

- "Lung markers" TTF-1, Napsin, p40, (CK5)
- "Mesothelioma makers" Calretinin, Popoplakin, WT1, CA125
- "Adrenal cortic.markers" Inhibin, Melan A, Synaptophysin
- Germinal cell markers SALL4, OCT3/4, PLAP, AFP, CD117, CD30
- Prostate markers NKX3.1, PSA, Prostein, AMACR, ERG
- Urinary tract markers Uroplakin II, GATA3, (CK5, CK20)

NordiQC Workshop in Diagnostic Immunohistochemistry

Culture & Congress Centre

2nd – 4th October 2019



AALBORG UNIVERSITY HOSPITAL

The unknown primary